343

BRAIN
VOL. 71, PART 4.

OLIVO-PONTO-CEREBELLAR ATROPHY

BY
MACDONALD CRITCHLEY AND J. G. GREENFIELD
(From the National Hospital, Queen Square)

PART I

THE opportunity of studying two verified cases of olivo-ponto-cerebellar atrophy suggested a scrutiny of the more general problem of the nature of the cerebellar degenerations and, in particular, the relationship of the clinico-pathological subtypes one with another.

Early in the nineteenth century a few instances of cerebellar agenesis had been noted, mainly as anatomical curiosities, devoid of clinical detail. Combette (1831) was one of the first to record such a condition; while Nothnagel (1879) was able to collect eleven such cases. Later the picture of a cerebellar atrophy became largely associated with the juvenile or adolescent forms of familial ataxia, as had been collected by Marie (1893) and entitled "heredo-cerebellar ataxia." Marie's observations were entirely clinical, however, and in the absence of pathological evidence, a condition of cerebellar atrophy was merely assumed. The status of Marie's heredo-cerebellar ataxy was assailed later on other grounds; as by Gordon Holmes (1907) who believed that Marie's cases were heterogeneous and not uniform, and that the title had become a mere pigeon-hole.

During the latter part of the eighteenth century morbid anatomists had also noted that at post-mortem examination a unilateral cerebellar shrinkage might occasionally be found in association with a long-standing lesion within the opposite cerebral hemisphere (H. C. Major, 1879; C. von Monakow, 1885; F. W. Mott and A. F. Tredgold, 1900). In such cases the cerebellar changes were unexpected, for no cerebellar signs or symptoms were demonstrable during life. Thus arose the conception of a "crossed atrophy" of the cerebellum, R. Cornélius (1907); André Thomas and R. Cornélius (1907); J. Lhermitte and B. Klarfeld (1911); and G. B. Hassin (1935).

In 1900, however, the problem of cerebellar degeneration was clarified

somewhat by a record made by Déjérine and André Thomas. These authors published two case-reports, the first of their patients dying so that pathological study was possible. Clinically, both patients had developed in late middle life—out of a normal personal and family background —a progressive cerebellar dysfunction affecting the legs first, and later the arms. Arterial degeneration and hypertension seemed to play no part. At the autopsy on the fatal case, a shrinkage of the cerebellum and of the middle cerebellar peduncle was obvious to the naked eye. Histologically there was a primitive cellular atrophy of the cerebellar cortex, the hemispheres being more affected than the vermis; disappearance of most of the projectional fibres; and an atrophy of the inferior part of the bulbar olives and of the pontine nuclei. The cerebellar nuclei were relatively intact.

Déjérine and Thomas concluded their paper with the following sentences: "There exists a cerebellar affection characterized anatomically by atrophy of the cortex, of the bulbar olives and of the grey matter of the pons, by the complete degeneration of the middle cerebellar peduncle and by partial atrophy of the restiform body, by the relative intactness of the central grey nuclei; it is a primary systemic degenerative atrophy, neither sclerotic nor inflammatory. Clinically, it is less well characterized —it shows itself as the cerebellar syndrome common to all the cerebellar atrophies. It is neither hereditary, nor familial, nor congenital, it comes on at an advanced age. Its ætiology is obscure. It belongs to the category of primary cellular atrophies. We refer to it under the term olivo-ponto-cerebellar atrophy."

The antecedent literature had no doubt held other records of this affection, such as, for instance, the report made by Pierret (1876); but to Déjérine and Thomas belongs the credit for establishing the disease as a clinico-pathological entity.

Following 1900 many other examples of olivo-ponto-cerebellar atrophy were reported, mainly as isolated instances, with or without pathological verification. But in some cases the morbid anatomy differed in certain important details from the disease described by Déjérine and Thomas, though the clinical picture had been very similar. Thus a type emerged where there was a simple outfall of Purkinje cells from the cerebellar cortex, without affection of the peduncles. Examples were recorded by Murri (1900), André Thomas (1905), Pierre Marie (1906), Italo Rossi (1907), La Salle Archambault (1916), Jelgerma (1919) and by Lhermitte (1922). Eventually this latter type of cerebellar atrophy was studied in detail by Pierre Marie, Foix and Alajouanine (1922) under the term "delayed cerebellar atrophy, predominantly cortical."

In 1907, Gordon Holmes published notes of a family in which cerebel-

lar symptoms came on at the age of 35 to 38 years in four siblings. Post-mortem examination showed cortical atrophy, affecting the Purkinje cells more than the granular layer and the upper (rostral) folia more than the lower (caudal) folia, but with no distinction between vermis and lateral lobes. The dorsal lamina of the inferior olive showed great loss of neurons, which the author attributed to a retrograde degeneration, i.e. a degeneration secondary to that of the cortex and involving only that part of the inferior olives which relayed to the more affected area of cortex. Similar cases of cerebello-olivary degeneration in which evidence of hereditary character was present were published by Hänel and Bielschowsky (1914); Akelaitis (1938); Parkes Weber and Greenfield (1942); Hall, Noad and Latham (1941, 1945); and van Bogaert (1947). In most of these families the disease was very slowly progressive and many of the patients survived till 70 or older, but in Akelaitis' family it ran a much more rapid course and death supervened within two years of the onset of symptoms. Mental symptoms were prominent in this family but not in the others. The cerebellar degeneration was greatest in the upper folia or more diffuse in which case the olivary degeneration affected the whole of the nucleus.

In addition to familial cases sporadic examples of cerebello-olivary degeneration have been reported by Marie, Foix and Alajouanine (1922); de Haene (1937) and others. Although Kinnier Wilson (1940) used the term olivo-cerebellar degeneration for this group, we prefer the name *cerebello-olivary degeneration* believing that the degeneration of the inferior olives is secondary to that of the cerebellar cortex. It has been noted that this type of degeneration is frequently familial, but both pure cortical cerebellar degeneration and olivo-ponto-cerebellar degeneration may also occasionally be familial, although in a much smaller proportion of the reported cases.

Brouwer and Biemond divided cortical cerebellar degeneration into localized and diffuse types. According to their classification, the olives may be involved in both types but are more constantly degenerated in the localized form, whereas in the diffuse form there is more often degeneration of the dentate nucleus and superior peduncle. Believing that their "localized cortical atrophy" may extend to involve the major part of the cerebellar cortex, we prefer the name "cerebello-olivary" degeneration since cases with olivary degeneration rarely show either degeneration of the superior peduncle or spinal cord, and vice versa. Akelaitis' family indicates that the degeneration of the inferior olives is not limited to cases of long duration, and there are many examples of long-standing cortical atrophy in which no olivary degeneration has been found.

Any classification of different types of cerebellar degeneration must take account of borderland cases, such as two described by Schroeder and Kirschbaum in which cortical degeneration was associated with degeneration both of the inferior olives and the nucleus dentatus, but without degeneration of the middle pedunclè and nuclei pontis. These cases were included by the authors in the olivo-ponto-cerebellar group, but they seem rather to partake of the characters of both types of primary cortical atrophy. Further difficulties have arisen from the association with progressive cerebellar degeneration, of changes in the spinal cord on the one side and of the basal ganglia and subthalamic nuclei on the other. Greenfield (1934) reported two cases of "subacute spino-cerebellar degeneration" in which cortical atrophy affecting almost exclusively the Purkinje cells was combined with degeneration of the corpus luysii. In one case the superior cerebellar peduncle was also degenerated. In one case a tumour of the breast had been removed; the other patient died of bronchial carcinoma. The association of malignant disease with cortical atrophy of more chronic types has been noted before (Parker and Kernohan, 1933). Since that time cases of subacute cerebellar degeneration have been reported by Kennard (1935), Alessi (1940) and Brouwer and Schlesinger (1947) in cancerous patients, and Brouwer and Biemond have suggested that cortical cerebellar degeneration tends to run a more rapid course in patients who also suffer from malignant disease. Three further cases of spino-cerebellar degeneration associated with cancer have been examined histologically and will be published shortly.

But degeneration of spinal tracts appears also to be not very uncommon in cases of olivo-ponto-cerebellar degeneration and cases have been published by Thomas (1897), Schroeder and Kirschbaum (1928), Hassin and Harris (1936) and by Ley (1947). The last two were heredo-familial cases. The tracts subserving movement and equilibrium seem to be those affected, i.e. the dorsal columnus, especially the middle root zone of Flechsig, the direct spino-cerebellar tracts and the pyramidal tracts.

Of recent years, evidence has been collected of degeneration of the basal ganglia and extra-pyramidal system along with progressive cerebellar degeneration. In some cases such as that of Titeca and van Bogaert (1946) clinical evidence of cerebellar disease was suppressed by a preponderance of extra-pyramidal symptoms. The cerebellar degeneration in these cases has been either of olivo-ponto-cerebellar type (Titeca and van Bogaert) or cerebello-olivary type (van Bogaert and Borreman, 1947; van Bogaert, 1947). These three cases belonged to three different families in which other members were probably affected with progressive disease of the nervous system.

The picture thus emerges of a number of system diseases affecting

predominantly cerebellar afferent and efferent pathways and the cerebellar cortex. All tend in varying degree to be hereditary or at least familial, the cerebello-olivary cases being predominantly so, and in all there is a tendency towards degeneration of other nuclei and fibre tracts subserving movement, but not directly connected with the cerebellum, e.g. the dorsal columnus of the cord and pyramidal tracts, substantia nigra, corpus luysii and lenticular nucleus. In some, especially in the more acute or subacute cases, there is progressive dementia which may be associated with evident degeneration of the cerebral cortex. In this wider group the older types of progressive cerebellar degeneration are tending to lose their identity. The following two cases exemplify the conflict between the more rigid and the wider views of classification. The first is an example of the association of disease of the basal ganglia with cerebellar degeneration of the olivo-ponto-cerebellar type and the second a pure case of Déjérine and Thomas' disease.[1]

Part II.—Personal Cases

Case 1.—G. H., male. An educated and intelligent schoolmaster with an excellent health record began at the age of 54 years to show an increasingly unsteady gait. The family history was negative in respect of any nervous or mental affection. At 56, he began to suffer periodic "collapses," i.e. transitory feelings of helplessness, consciousness being retained—each one being followed by tremor of the left arm. These collapses occurred with increasing frequency so that the tremor became more or less established. By the time the patient had reached the age of 57, the arms and hands had become inco-ordinate and clumsy rendering it difficult to write. At the age of 58 he was admitted to the National Hospital, Queen Square, under the care of Dr. F. M. R. Walshe (16.8.45—5.9.45). His psychical functions were found to be normal except for a mild euphoria. The speech was slurred. There was a cerebellar type of ataxy involving all four limbs, the legs being more affected than the arms, and the left side more than the right. There was no nystagmus. A little tremor was visible in the tongue and there was some intention tremor in the upper limbs. Tone was described as normal. Sensory tests revealed no abnormality. His tendon-jerks were increased; abdominals present and plantars equivocal. The gait was reeling and the feet slapped the ground noisily. There was no sign of cardiovascular degeneration. The cerebrospinal fluid was normal both in pressure and composition; the blood W.R. was negative.

The following year the patient—now 59 years of age—came into the Royal Masonic Hospital (27.12.46—23.1.47) under the care of Dr. Critchley.

He was now unable to stand, let alone walk. His mentality was not impaired—he was in the throes of writing a book—but he was unduly introspective and had prepared a typewritten autobiographical account of his illness running into very many foolscap pages. It was difficult to say whether or not he was euphoric. His

[1]Under the term "olivo-rubro-cerebellar atrophy" Lhermitte and Lejonne (1907) described a single case record where clinically cerebellar and extra-pyramidal symptoms were related to the pathological picture of a mixed affection of the superior cerebellar peduncle and of the red nuclei. The brain-stem, however, contained a focus of vascular softening which detracts seriously from any conception of a pure systemic degeneration; indeed in the course of the subsequent forty years no other case of an olivo-rubro-cerebellar atrophy has been identified.

speech was so impaired as to be virtually unintelligible. It was grossly slurred, jerky, forced, and at times explosive. It corresponded with what had been termed, inaccurately, "inspiratory speech," or what has been described as "spastic dysphonia." The words sounded as though he were talking while being throttled.

The neurological condition had deteriorated and there were some fresh developments. Nystagmus, for example, was well marked, being slower on looking to the left. The muscle tonus was now everywhere increased and showed the cogwheel variety of rigidity. There was a static tremor of the hands, especially the left, increased on volitional movement. Tendon reflexes were still exaggerated, and the plantar responses were now probably extensor in type. Incontinence of urine and fæces was now a prominent symptom.

During the next few weeks his condition rapidly deteriorated. Bulbar (or pseudobulbar) manifestations arose, with anarthria, dysphagia, salivation and emotivity. Extrapyramidal features were even more conspicuous and the combination of an expressionless face, an immobile posture of flexion, with poverty of movement, extreme slowness of movement and rigidity, now dominated the clinical picture.

While in this state he died in his sleep (23.1.47). Clinically, the diagnosis had been made of one of the presenile cerebellar degenerations, either olivo-ponto-cerebellar atrophy, or else the late cortical cerebellar atrophy.

A post-mortem examination was carried out by one of us (J. G. G.), with the help of the house-physician (Dr. Jackson), about forty-eight hours after death.

The body was well nourished with an abdominal wound for suprapubic cystotomy.

Thorax.—There was œdema and congestion of all lobes of the lungs but it was most severe in the lower lobes where there were areas of early consolidation. The bronchi contained frothy mucus. The heart was rather flabby, but otherwise normal. The liver, spleen, pancreas, kidneys, stomach and intestines showed no gross abnormality and the bladder did not reveal any evidence of infection.

The brain and spinal cord were removed completely. The cerebral hemispheres were of normal appearance but there was flattening of the lateral surfaces of the pons and the inferior olives were less prominent than normal. The cerebellum was smaller than normal and felt soft.

The vertebræ seemed soft, and there was a partial crushing of the body of the second lumbar vertebra.

Histological examination.—Sections of various parts of the cortex, the basal ganglia, brain-stem, cerebellum and spinal cord were made after embedding in celloidin. The staining methods of Nissl, Mallory (phosphotungstic acid hæmatoxylin), Gros-Bielschowsky, Loyez (iron alum hæmatoxylin for myelin) and van Gieson with iron alum hæmatoxylin were used.

Cerebellum.—There was pallor of myelin staining in the white centres of the folia both in the vermis and lateral lobes. It was greater in the upper (rostral) half of the vermis than in the lower (caudal) half, but was present in both. In the lateral lobes the tonsils were relatively spared (fig. 1). This pallor of myelin staining was associated with a corresponding diminution in the numbers of axons as seen in the Gros-Bielschowsky stain. It was not therefore a periaxial degeneration of myelin such as has been postulated in this form of cerebellar degeneration. In all affected parts of the cortex there was a degeneration of granule cells which resembled that seen in hyperglycæmia, i.e. a pallor and irregular shape in many of the nuclei and disappearance also of many. The Purkinje cells were also diminished in numbers and many empty baskets were present and in both the upper vermis and the lateral hemispheres many axonal swellings ("torpedoes") were present in the granular layer. The degree of gliosis of the molecular layer corresponded to the degree of loss of Purkinje and granule cells in that area, but there was little

or no shrinkage of this layer. In all respects there was very little difference between the lateral lobes and the upper part of the vermis, indeed there appeared to be more "torpedoes" in the latter situation. Nor was there any marked difference between the two hemispheres.

In the *nucleus dentatus* there was some increase in the number of microglial nuclei and a general slight increase in neuroglial fibres. There was no definite evidence of loss of neurons here.

In the *medulla,* the chief abnormality was cell loss and gliosis in the inferior olive (fig. 2). All parts were affected, but there was rather more neuronal degeneration in the more rostral than in the more caudal parts of the nucleus, and perhaps slightly more in the dorsal than in the ventral folia of the nucleus. All the neurons were shrunken, and had lost their Nissl granules, appearing as pale glassy bodies with a variable amount of lipoid. Owing to their small size and lack of staining properties they appeared to be fewer in number than a more careful examination showed them to be, but there was undoubtedly considerable cell loss also (fig. 4). The gliosis was associated both with a great increase in density of the feltwork of neuroglial fibrils, and with swelling and increase in number of astrocyte nuclei. There was, however, no great loss of nerve fibres in the hilum of the olive, although the myelin staining here was rather paler than normal.

In the *pons* there was considerable pallor of myelin staining in the transverse fibres, especially in the lower half of the pons and this was associated with loss of many of the neurons of the nuclei pontis, which were replaced by astrocytes (fig. 3). There was considerable variation between the different groups of neurons, but no definite systematization of the cell loss was made out except that it was greater in the lower half of the pons.

The *mid-brain* showed no evident degeneration. The *nucleus ruber, substantia nigra,* and *corpus luysii* appeared to be unaffected.

Sections through the *thalamus* showed a very severe loss of neurons in the *centromedian nucleus.* On the right side this appeared to be almost complete, only a few shrunken palely staining remnants of nerve cells being seen (fig. 6). The cell loss was not associated with any evident loss of myelinated fibres nor with more than the slightest gliosis. On the left side the chief loss was in the medial half of the nucleus, and even here many cells showed only slight degeneration whereas in the lateral half many normal cells were present. There appeared, however, to be fewer neurons here than normal. No changes resembling axonal reaction (central chromatolysis) were seen.

In the *putamen* on both sides loss of neurons and gliosis of fibre-forming cells was seen in certain areas (fig. 5). In sections stained by Nissl's method abundant astrocyte nuclei were seen, many in pairs or fours and many were surrounded by an irregular zone of greenish granules, probably lying in their processes. In such areas there was some loss of the smaller neurons and degeneration and probably some loss also of the large nerve cells. The areas most affected were, on the right side, the middle third of the putamen in its anterior half and the upper three-quarters in its posterior part. On the left side the degeneration and gliosis was on the whole of less severity and was limited to the upper half of the nucleus, especially in its outer part in the anterior half of the nucleus, and the upper half or two-thirds of the nucleus in its posterior half. On the left side the gliosis extended into the upper half of the outer segment of the globus pallidus, but no obvious loss of neurons was seen here.

The condition of the upper half of the putamen on both sides resembled that seen in hepatolenticular degeneration in that there was an obvious increase of cells most of which were astrocytes, but the degeneration of the small neurons made it difficult to tell with Nissl's stain which were astrocytes and which neurons. However, the strong fibres passing from the astrocytes, as seen with Mallory's phos-

photungstic acid hæmatoxylin, clearly distinguished the astrocytes, which showed some fibrous gliosis also in areas where there was no evident loss of neurons. The *globus pallidus* showed no cell loss and gliosis only in the neighbourhood of the most affected areas of the putamen.

In the *nucleus caudatus* the only abnormality was an excess of astrocyte nuclei, with several paired nuclei surrounded by greenish granules. Fibre-forming astrocytes were only seen under the wall of the ventricles.

The *cerebral cortex* in the areas examined showed no abnormality.

Summary of pathological changes.—This case thus shows the picture of olivo-ponto-cerebellar atrophy in a rather atypical manner. While there was atrophy of the inferior olives and nuclei pontis the degeneration in the cerebellum was equally great in the upper half of the vermis and in the lateral lobes. There was also a tendency in the latter for the degeneration to be greater in the upper than in the lower convolutions, but the difference was not so great as in some long-standing cases of hereditary cerebello-olivary degeneration nor was the degeneration of the olives limited to the dorsal foliæ. In addition there was a progressive degeneration and gliosis of the putamen, and neuronal degeneration in the centromedian nucleus of the thalamus which may have been due to the putaminal degeneration.

Case 2.—M. B., female, was admitted under the care of Dr. Grainger Stewart to the National Hospital, Queen Square, on 2.1.36 where she died on 4.2.36.

The family history was without neuropsychiatric significance. Her previous personality and health had shown no noteworthy features.

At the age of 49 she began to suffer from sudden but momentary attacks of giddiness in which she was apt to fall, but without losing consciousness. They gradually increased in frequency but after about a year ceased altogether. About this time her memory began to fail. Soon after the onset of these attacks she became unsteady when standing or walking. This imbalance increased so that by the time she entered hospital at the age of 54 she could get about the house only by dragging herself from one piece of furniture to another. Otherwise, she would crawl across the floor like an infant.

One year before the onset of giddiness and unsteady gait, her speech became indistinct, a disability which increased steadily. By the age of 54 her voice had become high-pitched and she developed a curious inspiratory crow.

At 52 years she noticed double vision on occasions; nocturnal enuresis also showed itself at this time, while rectal incontinence did not develop until two years later, that is, a few days before admission to hospital.

In hospital she appeared fatuous and contented, quite indifferent to the fact that she was frequently passing urine and fæces in the bed. She was a poor witness and co-operated badly. The speech was impaired in an unusual fashion. She spoke slowly and jerkily in a syllabic manner, with exaggerated head and facial movements. Great variations in the pitch and in the volume of sound rendered the speech barely comprehensible. Some words were enunciated normally; some would be bellowed; most would be emitted in a high-pitched and explosive whisper. Though the pitch of the speech was usually high, it might suddenly alter in the middle of a phrase and become low and croaking.

A loud crowing sound often accompanied inspiration especially when the patient was asleep.

A gross cerebellar type of ataxy was demonstrable in the limbs which interfered considerably with volitional activity. There was no great alteration in tonus.

Nystagmus was demonstrable on lateral gaze being more marked to the right. Her knee and ankle jerks were exaggerated, and while the left plantar response was flexor in type, stimulation of the extreme outer edge of the right foot evoked a probably extensor movement of the great toe.

Her gait was bizarre; she needed the support of two attendants and even then reeled wildly.

There was no sensory defect. Motor power in the limbs was limited only by the cerebellar defect. Palatal elevation was minimal on phonation, and the ocular movement of convergence-accommodation was impaired. No signs of cardiovascular disease could be detected.

The spinal fluid was normal in pressure (105 mm. water) and apart from an increase in protein (0·080 per cent.) showed no abnormality in composition.

The post-mortem examination was performed about twenty-four hours after death.

The body of a well-preserved, middle-aged woman showed no external evidence of disease.

On removing the calvarium, the dura mater was found to be normally tense over the cerebral hemispheres, but very lax over the cerebellum which was seen after removal of the dura mater to be very shrunken so that its posterior limit was an inch in front of the occipital poles (fig. 7). The pons as seen from the ventral aspect was very shrunken and yellowish. The arteries at the base were perfectly healthy and thin walled. The anterior cerebral artery was abnormal, however, in that a single callosal branch arose from the anterior communicating artery.

The organs of the body cavity showed no evidence of disease except some congestion of the bases of the lungs. After fixation of the brain, slices from various areas were embedded in celloidin and stained either by the Weigert-Pal method (Wolter's modification) or by iron hæmatoxylin with van Gieson's counter stain and by Nissl's method. These showed no evidence of disease above the level of the pons. At this level, however, there was very marked shrinkage of the ventral half, and microscopically there was almost complete disappearance of the neurons of the nuclei pontis which were replaced by astrocytes and microglial cells. The transverse fibres of the pons were also severely atrophied and the middle peduncles were shrunken and demyelinated. The only myelinated fibres seen ventral to the fillets in the pons were the vertically coursing cortico-spinal and cortico-pontine fibres.

The *cerebellar hemispheres* showed considerable loss of Purkinje cells and thinning of the granular layer with accentuation of the line of Bergmann astrocytes and gliosis of all the layers (figs. 9 – 10). The white centres of the convolutions were severely demyelinated in the lateral hemispheres where only sparse myelinated fibres were seen. Rather more fibres appeared in the white matter of the vermis, although here also the number of fibres was much less than normal. A greater density of fibres was seen in the capsule of the nucleus dentatus and a normal quota in its hilum. In the flocculus the myelination was almost normal. In the medulla there was considerable shrinkage of the olive, but this shrinkage was less striking than the almost complete loss of myelinated fibres from its hilum which was seen in Weigert-Pal sections (fig. 8). The internal arcuate fibres from the dorsal column nuclei and the radicles of the hypoglossal nerve were almost the only fibres seen passing through the olives in their upper part. In their lower half there was a fair number of fibres in the hilum but a considerable diminution of the network in the folia.

Sections for cell stains were taken at an intermediate level and therefore probably did not represent the most severely affected (upper) level of the olivary nuclei. But even here there was almost complete disappearance of all the neurons, less than ten being seen in the total cross section of one olive, and these were shrunken. The areas of the folia were shown up by an excess of astrocytic and

microglial nuclei. No abnormality was seen in sections of the spinal cord examined by myelin or cell stains.

Part III—Clinical Manifestations

During life it was clearly not possible to decide with confidence to which of the two chief representatives of the presenile cerebellar degenerations our cases belonged. The exact diagnosis could ultimately be established only by post-mortem study.

The question now arises as to whether, as a matter of fact, it is reasonable to make the diagnosis of the olivo-ponto-cerebellar type of atrophy on clinical grounds alone. Furthermore, whether one can distinguish at the bedside such patients from cases of delayed cortical cerebellar atrophy. This twofold problem demands a scrutiny of cases recorded in the literature coupled with these two personal cases. In such a task it is wise to eliminate entirely from the analysis all cases without anatomical verification. A number of heterogeneous, atypical and incomplete cases, are thereby excluded and the clinical picture becomes more clear-cut.

Both males and females are affected in approximately equal numbers. The age of onset is usually between 47 and 57; instances of exceptionally early onset are on record but are unsupported by pathological study (e.g. G. Guillain, A. Thévenard and Jonesco, 1928). Similarly, cases starting in old age probably represent some form of degeneration other than olivo-ponto-cerebellar atrophy, and the likelihood of a vascular basis is great.

In the majority of cases the picture of olivo-ponto-cerebellar atrophy arises *de novo* out of a normal family history, and genetic factors seem to play no role. Superficial acquaintance with the literature may at first suggest otherwise. The familial cases, recorded first by W. Keiller (1926) as Marie's hereditary ataxia, were at the time purely clinical observations; later some of the members died and the brains were studied by G. B. Hassin and T. H. Harris (1936). Though these authors made the pathological diagnosis of olivo-ponto-cerebellar atrophy, their conclusions are far from convincing. A familial incidence of the disease seems to have been established pathologically in the case of two brothers, one of whom was recorded by C. Winkler (1923) and the other by G. Hoeneveld (1923). In 1939, V. Gallemaerts, F. Kleyntjens and W. Cloetens, demonstrated two brothers suffering clinically from a Marie's type of heredo-ataxia starting at about the age of 30. Subsequently R. A. Ley (1947) was able to study the morbid anatomy of one of those patients and found the changes of that rare variety of olivo-ponto-cerebellar atrophy with spinal involvement —reminiscent of Friedreich's disease. Instances of neuropathic or psychopathic stock have also been noted by some who have written on the subject of olivo-ponto-cerebellar atrophy (e.g. C. Davison and J. S. Wechsler, 1938), but in every case the diagnosis is unsubstantiated by pathological evidence.

We may merely refer to the familial occurrence of cerebellar agenesis described by Finley and B. Brouwer (1935) in cats, the anatomy of which was not unlike that of olivo-ponto-cerebellar atrophy in man.

An important negative feature in the ætiology of olivo-ponto-cerebellar atrophy is the lack of any obvious general morbid condition such as for instance arteriosclerosis, or any recognizable toxi-infective agency. Injury, too, seems to play no part in the development of this affection. The question of an abiotrophic process raises the enquiry as to the occurrence of any other sign which may be regarded as an involutional change; here again clinical experience can point to no definite marks of premature ageing in any other system of the body.

The march of the affection is usually one of steady progression; the interval between the appearance of the first symptoms and death is commonly a matter of years, usually between four and six.

The earliest symptom usually consists in an impairment of balance noticed while walking or standing. An unsteady gait is then one of the first manifestations and is not only recognizable by the patient himself, but is apparent to others. In both of the personal cases here recorded, frequent falls ("collapse") were noted at the outset of the malady, and these may be ascribed perhaps to inco-ordinate action of the legs, or possibly to sudden spells of vertigo. Disordered walking may constitute the only trouble for many months, the disability gradually increasing.

Impaired articulation, at first quite slight in degree and often unnoticed by the patient, may follow the ataxia. A little later, tremor of the hands may be described often as an intentional type and often accompanied by maladroitness in finger movements.

For two or three years these two symptoms, ataxia of the limbs and dysarthria, may constitute the whole of the patient's description of his disability, the clinical picture evolving insidiously and developing slowly. Later symptoms include weakness of the legs, often accompanied by rigidity, and leading to a bedridden state; a consciousness of increasing mental inefficiency; imperfect sphincter control, the bladder being affected before the rectum; and lastly such bulbar symptoms as salivation and dysphagia. Throughout the illness pain, cramps, subjective dysæsthesia, ocular or visual defect, typically do not occur.

The foregoing remarks refer to the subjective complaints preferred by the patient. Routine neuropsychiatric examination will display a wealth of objective disorders, which for purpose of description may be discussed under four main headings, viz. (1) psychological, (2) dysarthria, (3) cerebellar signs, and (4) extrapyramidal manifestations.

(1) *Psychological changes* are not uncommon, but not invariable. Intellectual deterioration may be present and may at times amount to a

conspicuous dementia (Schultze, 1887; Fickler, 1911; Schroeder and Kirschbaum, 1928; van Bogaert and Bertrand, 1929). In the confirmed case recorded by van Bogaert and Bertrand, mental symptoms preceded neurological signs, and dominated the clinical picture throughout. An apathy went rapidly on to a dementia which was punctuated by agitation and maniacal outbursts. Fickler's case was more complicated in that both diabetes and alcoholism were present before signs of cerebellar degeneration appeared.

In the original case recorded by Déjérine and Thomas the intellectual faculties were said to have deteriorated as the patient grew feeble. Brouwer and Biemond also spoke of psychical disorders as "common," including depression as well as dementia. These authors referred particularly to the case reported by Carp where there were conspicuous changes in the frontal and temporal areas of the cerebellar cortex. Emotivity was noted in the patient described by O. Luque and R. P. Morcillo (1945). In the complicated case recorded by Titeca and van Bogaert where pallido-luysian disease was also present, the patient showed a paranoia and later a dementia.

Of our two patients it may be said that the first one showed no gross intellectual falling off. There was perhaps some euphoria in the first year or two of his illness, later replaced by an unusual degree of introspection. Our second patient certainly displayed a mild dementia, with impaired insight into the nature and gravity of her plight.

(2) *Disorders of articulation* occur early in this disease; they are rarely if ever absent from the symptomatology; they usually become very marked indeed and often are of a grotesque and unusual character.

Reference to the literature betrays many differing descriptions of the speech impairment. Déjérine and Thomas described the speech of their patient as being slow and somewhat staccato, the teeth being kept in apposition and the lip movements being feeble in range. As the patient went downhill the speech became slower, more difficult and scanning. The patient of van Bogaert and Bertrand spoke slowly with a scanning rhythm; the voice was hushed, guttural and "bramée." Guillain, Thévenard and Jonesco (1928) noted in their patient—a presumed but uncorroborated case of olivo-ponto-cerebellar atrophy—that the speech would become progressively worse the longer she spoke.

Jelgerma described the speech in his case in the words: "le malade mache ses mots, après quoi il les crache." ("The patient chews his words and then spits them out.")

The most interesting type of speech disorder, however, is one which is conspicuous on account of a peculiar strained quality, as if the speaker were being throttled. In the past this has received many descriptive epithets:

"inspiratory speech," "sea-lion speech," and so on. It was described by Critchley (1939) under the term "spastic dysphonia." Of the three patients reported in that communication, one suffered from a variety of cerebellar degeneration, but in the absence of pathological verification it cannot be said whether or not the case was one of olivo-ponto-cerebellar atrophy. P. Schuster (1924) had previously recorded five patients whose speech affection was of this type where the neurological diagnosis was also that of a cerebellar degeneration. There was, however, no autopsy confirmation of that diagnosis in any instance.

Of the two patients here recorded, the speech was in one case, for a time at any rate, recognizable as an instance of spastic dysphonia. Later, it deteriorated and became more and more "bulbar" in character. The other patient (Case 2) showed not so much a disorder in the correct pronunciation of the consonants, as an extreme variability in both pitch and volume. There resulted a series of utterances which were barely intelligible.

(3) *Cerebellar disorders* are, of course, one of the most conspicuous features of this disease, especially in the early stages, for later the hypotonus —and other manifestations—may be concealed by associated extrapyramidal motor signs. The cerebellar signs include nystagmus on ocular deviation; a characteristic dysarthria; static tremor of the upper limbs and at times of the head; inco-ordinated with intention tremor, dysmetria and dyssynergia; reduction of tonus with characteristic cerebellar postures of the head and neck and of the upper limbs; slight reduction in motor power with considerable disturbance in the execution of rapid movements, alternating movements or finger manipulations; pendular knee-jerks.

Special note is deserving as to some of the foregoing points. Nystagmus appears relatively late, and may not be demonstrable in about half of the patients observed clinically. On the other hand, nystagmus occurs still more rarely in cases of delayed cortical cerebellar atrophy. Its presence, therefore, is a clinical point of some importance in distinguishing the two varieties of cerebellar atrophy.

Static tremor of the head or limbs is often not demonstrable, in the early stages at any rate. Its presence may be of some importance, however, for at times it may appear to antedate other signs of olivo-ponto-cerebellar atrophy, for some years. Indeed, a diagnosis may have been made in the earliest stages, on the basis of tremor alone, of "idiopathic" or "essential" tremor. Although anatomical proof is as yet lacking, there are at least a number of clinical points to make question whether "essential" tremor may not, at times at any rate, represent an incomplete or a premature variant of one of the cerebellar atrophies.

Special tests for vestibulo-cerebellar mechanisms may reveal a disordered function. Thus, the patient placed in a hands-and-knees attitude may fail to show automatic associated defence movements when the bed on which he rests is suddenly tilted (Rademaker-Garcin test).

As in most of the cerebellar atrophies, the disordered function seems to show itself first in the legs, so that an ataxic gait may occur before the arms become inco-ordinate.

(4) *Extrapyramidal symptoms* were first recorded in this affection by von Stauffenberg (1918). They usually appear somewhat late in the course of the disease though Z. Messing's case (1930) may be an exception here. Messing had under his care a female Parkinsonian who died at the age of 62 having been ill for five years. At the autopsy a marked atrophy of the ponto-cerebellar system was an unexpected though conspicuous finding.

Ordinarily the cerebellar hypotonus becomes slowly replaced by a pallidal type of rigidity. An increasing poverty of movement together with slowness of mobility is associated with an attitude of flexion and an expressionless facies. Guillain, Thévenard and Jonesco described under the term "hypertonie d'effort" a type of extrapyramidal rigidity in a case of olivo-ponto-cerebellar atrophy, which would become intensified by any voluntary movement.

P. Mathieu and I. Bertrand (1938) made a special note of this association. They declared that in addition to a pallidal rigidity, there may develop a Parkinsonian-like tremor. Or a cerebellar static tremor may later take on Parkinsonian features. Catatonic signs may also be demonstrable. According to these writers, in the development of cerebellar atrophy with delayed rigidity, there is first a stage of hypotonus and passivity, then a period when hypotonus at rest is associated with an effort hypotonus, and eventually a permanent plastic hypotonus is evolved.

In Titeca and van Bogaert's case a unilateral hypotonus and hemiballism complicated the picture. Their case was an unusual one, however, for the pathology comprised a pallido-luysian abiotrophy, together with a dentato-rubral system affection, alongside the changes of an olivo-ponto-cerebellar atrophy.

(5) *Additional manifestations* which may occur include abolition of the tendon reflexes, pyramidal signs, and sphincteric incontinence.

It is sometimes found that the tendon-jerks in the lower limbs may become more and more difficult to elicit. Nicolesco (1936) who stressed this feature, associated it with associated pathological changes in the posterior column of the cord.

Signs of pyramidal disease may be noted during the late stages being

usually betrayed by extensor plantar responses. Some of the hypotonus, and the frequent liveliness of the tendon-jerks may in part be due of course to pyramidal as well as extra-pyramidal dysfunction.

Urinary incontinence is a relatively early symptom and is of some importance in distinguishing the olivo-ponto-cerebellar type of atrophy from the Marie-Foix-Alajouanine variety. Rectal incontinence may also occur, though usually at a later stage.

Among the negative points in the symptomatology may be mentioned the absence of sensory changes, of visual symptoms, and of muscular wasting. In view of the characteristic pathological involvement of the pons it is noteworthy how rarely one encounters cranial nerve affections in this disease.

Part IV.—The Nature of Olivo-Ponto-Cerebellar Atrophy

For some years the opinion has been held that olivo-ponto-cerebellar atrophy represents an abiotrophy of the neocerebellum; or to express the matter differently, an atrophy of the cerebellipetal systems. Other writers, without necessarily disagreeing with either of these conceptions have stressed the embryological aspect; they have pointed out that the so-called "cell-bands" described by Essick (1907, 1909 and 1912) which migrating from the rhombic lip, or Rautenlippe of His, form the corpus ponto-bulbare, or common ancestor of the structures involved in this disease. In this way olivo-ponto-cerebellar atrophy might be designated as an abiotrophy of the derivatives of the cell-bands of Essick.

Perhaps the foregoing conceptions are too schematic, and they do not altogether explain some of the cases complicated by lesions elsewhere. A number of questions arise for discussion:

(1) Where does the pathological process start? In the cerebellar cortex, or in the olivo-pontine nuclei, or both simultaneously?

(2) Are the fibres affected before the grey matter (as von Stauffenberg suggested)?

(3) Are the Purkinje cells necessarily involved?

These three points were raised specifically by van Bogaert and Bertrand. Other questions also naturally arise:

(4) Are there incomplete variants of the syndrome of olivo-ponto-cerebellar atrophy, and, if so, where do they fall?

(5) What relationship exists between olivo-ponto-cerebellar atrophy, and the purely cortical or cerebello-olivary types of degeneration.

(6) What is the significance of the lesions which have at times been

found in structures outside of the cerebellipetal system, e.g. the pallidum, thalamus, corpus-luysii, locus niger, cerebral cortex and spinal cord?

(7) What part does the syndrome of olivo-ponto-cerebellar atrophy bear in relation to Marie's heredo-cerebellar ataxia?

(1) van Bogaert and Bertrand would answer the problem of the site of origin of the atrophy by implicating the grey substance of the pontine nuclei, the olives, the arcuate nuclei, and the lateral and reticular nuclei. Shortly afterwards the middle cerebellar peduncle shows degenerative changes as well as its arciform connections. At this stage the cerebellar cortex is intact.

(2) The same authors also claim that the myelinated fibres are affected primarily. Scherer (1933) who had the opportunity of studying the pathology of five cases of olivo-ponto-cerebellar atrophy succumbing at different stages of evolution, also believed that the affection starts in the white matter. He considers that demyelination and a fibrous glial proliferation occur together and that they show themselves first in the peripheral lamellæ of the ventro-caudal parts of the hemispheres, i.e. the superior and inferior semi-lunar lobes. The disease process thus follows inversely the order of myelination in the fœtus. There is little evidence that the degeneration in the cerebellar white matter is "periaxial" in character, i.e. that the myelin sheaths are affected at a definitely earlier stage than the axis cylinders. Both appear to us to degenerate at the same time. But as observed by Greenfield (1934) in spino-cerebellar degeneration there is some evidence that in this group of diseases the nerve fibres may die back from their periphery towards their cell body. The "torpedoes" commonly found on the axons of the Purkinje cells are explicable only on this basis. In our first case, the degeneration of the white matter of the folia appeared to be disproportionate to the loss of Purkinje cells and of neurons of the nuclei pontis combined. But it is impossible to dogmatize on this matter owing to the wide distribution of both the main types of neuron from which the fibres in the white matter take their origin.

(3) Purkinje cells may, of course, be affected to some extent or they may remain intact. Bakker (1924) has regarded the Purkinje cells as derivatives of the embryonic region of the dorsal nuclei of the eighth nerve; in that way they are to be associated with Essick's cellular bands. Difficulties therefore arise in explaining why the Purkinje cells should not always be involved. van Bogaert and Bertrand prefer to regard the occasional implication of the Purkinje cells as a trans-synaptic degeneration secondary to a lesion of the cerebellipetal fibres. This view does not differ from that expressed earlier by C. Winkler (1923) who believed that a certain number of synapse-cells, and of Purkinje cells, might participate

in the system degeneration responsible for olivo-ponto-cerebellar atrophy.

(4) Hassin and Harris regarded the cerebello-olivary degeneration as an incomplete form of olivo-ponto-cerebellar degeneration. It is of course possible to argue that all forms of cerebellar degeneration belong to one disease group, but the number of familial cases in which the degeneration has affected only the cerebellar cortex and the corresponding part of the inferior olives is too large to allow these cases to be considered as incomplete forms of the Déjérine-Thomas disease. On the other hand there are cases of ponto-cerebellar type (Messing) or of olivo-pontine type (Bertrand and Brouwer) which cannot be placed in any other category, and Titeca and van Bogaert are probably right in including their family in this group, although the brunt of the disease fell on the pallido-luysian system in the case in which histological evidence was available.

(5) We have already discussed this question to some extent. Although at first sight there seems to be little relationship between the cerebellipetal degeneration of olivo-ponto-cerebellar disease and the cerebellofugal cortical atrophies, we have seen that the spino-cerebellar tracts may be affected in both; in other words, the distinction between cerebellipetal and cerebellofugal degenerations is somewhat academic. As is well known olivary degeneration may result from degeneration of the tegmental tract and from lesions in the region of the nucleus dentatus; that is from damage to tracts both going to, and leaving, the olives so that one might expect degeneration to spread in the tracts connecting the cerebellum to the brain-stem in both directions. Similarly it would appear on the available evidence that while the degeneration of the olives is primary in olivo-ponto-cerebellar atrophy, it is secondary to disease of the cerebellar cortex in cerebello-olivary degeneration. It remains true, however, that most cases of progressive cerebellar disease fall more or less into one or the other group; and, so far as we know, no family has been recorded in which the disease has presented different pathological types in different affected members.

(6) Before accepting any conception of a pure cerebellipetal (neocerebellar) abiotrophy one has to discuss and explain the existence of pathological changes outside that particular system. As already stated, neighbouring lesions may well be accounted for upon the basis of a trans-synaptic or trans-neuronal degeneration (e.g. Purkinje cells, dentatus). Such a view does not satisfactorily explain degenerations within the prefrontal, frontal or temporal cortex (Fickler, Carp, van Bogaert and Bertrand); the spinal cord (Hassin and Harris, Nicolesco, Ley); the basal ganglia and locus niger (Scherer); thalamus (Noica, Nicolesco and Banu). In the recent and unusual case recorded by Titeca and van Bogaert, extensive changes were found in the dentatum, red nucleus, corpus luysii

and pallidum in addition to the cerebellipetal atrophy. Their case was also apparently familial in its incidence. The authors believed that their case bridged a gap between olivo-ponto-cerebellar atrophy and the various degenerations of the thalamo-striatal systems. Marburg and W. Riese (1947) believe that a common vascular supply, by which a noxa might spread to structures outside the olivary and cerebellar systems, may be responsible. Under the title "chronic progressive spino-cerebello-cortical lipodystrophy affecting certain arterial supply areas" they described a disease-entity resembling both Friedreich's and Marie's disease with the addition of cortical involvement. The morbid anatomy comprised a progressive degeneration of Goll's tract, the border zones of the lateral funiculus, the cerebellum, olives and pons, and the frontal cortex.

(7) Case 1 here published is a further example of the association of striatal disease with olivo-ponto-cerebellar atrophy. But the recently published familial cases of van Bogaert (1947) and van Bogaert and Borreman show that striatal disease may be associated also with cerebello-olivary degeneration. Thus while it appears that Déjérine-Thomas' disease is more often associated with degeneration of spinal cord and basal ganglia than the more purely cerebellar types, it has no monopoly in this matter. We do not accept the view of Hassin and Harris who have written . . . "studies of the three cases and of the literature permit a conclusion that heredo-cerebellar ataxia and olivo-ponto-cerebellar atrophy are one disease process." And again . . . "careful analysis of the cases recorded as instances of heredo-cerebellar atrophy of Marie forces one to the conclusion that practically all such cases may be considered cases of olivo-ponto-cerebellar atrophy." The family studied by these authors and Keiller was unusual in several ways, not least in that it was of negro descent. But as has been seen, this is not the only familial instance of olivo-ponto-cerebellar atrophy. Hassin and Harris were, however, able to make this generalization only by including familial cases of cerebello-olivary degeneration as formes frustes of Déjérine-Thomas' disease, a point of view which receives no warrant from the literature. As has been seen, the clinical picture of hereditary cerebellar ataxia has been found to be based on cerebello-olivary degeneration in the great majority of families. The evidence for an hereditary transmission of purely cortical cerebellar degeneration rests on the single family of Richter (1938), as in the older cases of Fraser and of Nonne, instanced by Brouwer and Biemond, the histological examination was very incomplete.

As clinical differentiation of the three types appears to be impossible, it seems certain that cases both of olivo-ponto-cerebellar and of cerebello-olivary type, along with some anomalous cases of Friedreich's ataxia, were included in Marie's hereditary ataxia.

PLATE XVI

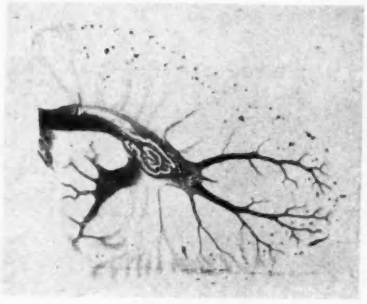


FIG. 1.

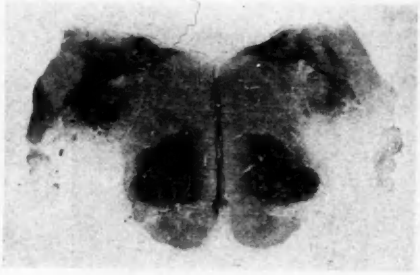


FIG. 2.

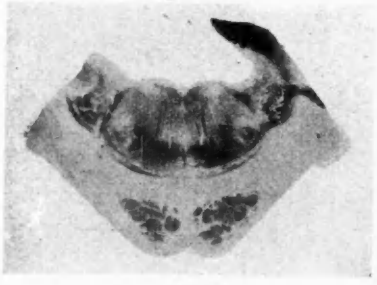


FIG. 3.

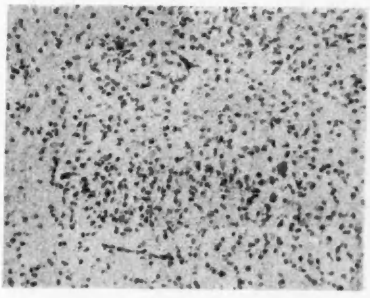


FIG. 4.

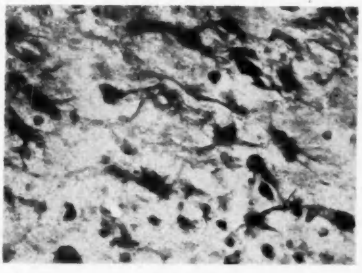


FIG. 5.

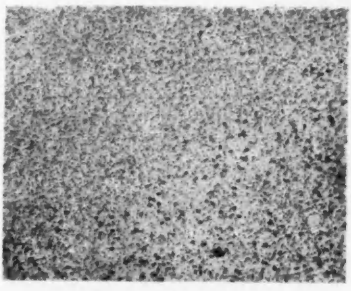


FIG. 6.

To illustrate article by ***Macdonald Critchley and J. G. Greenfield.***

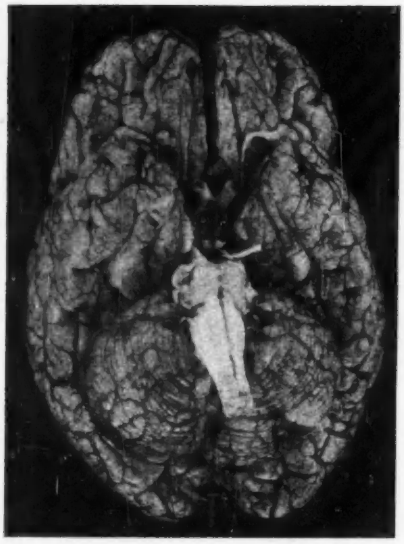


FIG. 7.

FIG. 8.

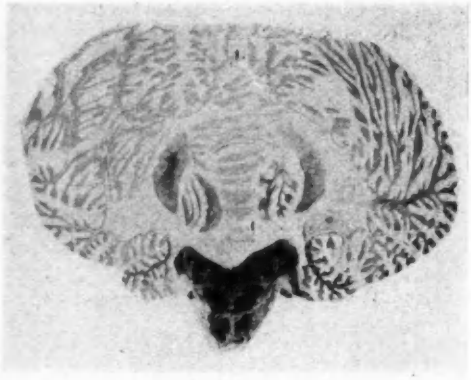


FIG. 9.

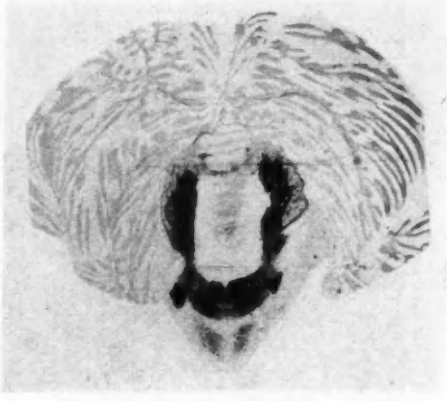


FIG. 10.

To illustrate article by Macdonald Critchley and J. G. Greenfield.

LEGENDS FOR ILLUSTRATIONS

FIG. 1 (*Case* 1).—Cerebellar hemisphere showing partial loss of myelinated fibres, especially in the upper folia, with sparing of the tonsil and of the superior cerebellar peduncle. Loyez' myelin stain.

FIG. 2 (*Case* 1).—Medulla, showing the intense fibrous gliosis of the olives. Mallory's phosphotungstic acid hæmatoxylin.

FIG. 3 (*Case* 1).—Mid-level of pons, to show the loss of transverse fibres and middle peduncle. Loyez' myelin stain.

FIG. 4 (*Case* 1).—Inferior olive. Nissl stain. There is considerable loss of neurons and no normal nerve cells remain, but many atrophic cells are still visible.

FIG. 5 (*Case* 1).—Fibrous astrocytic hyperplasia in the right putamen.

FIG. 6 (*Case* 1).—Right optic thalamus at the junction of the centromedian nucleus and the dorsomedian nucleus, to indicate the complete absence of neurons in the centromedian nucleus.

FIG. 7 (*Case* 2).—Base of the brain showing atrophy of pons, olives and cerebellum.

FIG. 8 (*Case* 2).—Medulla, showing complete loss of medullated fibres in the inferior olives. Weigert-Pal stain.

FIGS. 9 and 10 (*Case* 2).—Transverse section of lower and mid-pons and cerebellum (Weigert-Pal counterstained with carmine) to show the loss of myelinated fibres in the middle peduncle and cerebellar hemispheres with integrity of the flocculus, tonsils, vermis and superior cerebellar peduncle.

REFERENCES

AKELAITIS, A. J. (1938) Hereditary form of primary parenchymatous atrophy of cerebellar cortex associated with mental deterioration, *Amer. J. Psychiat.*, **94**, 1115 - 1140.

ALESSI, D. (1940) Lesioni parencymatose del ceribelletto da carcinoma uterino, *Riv. di Pat. nervosa e mentale*, **55**, 148 - 174.

ARCHAMBAULT, LA SALLE (1918) Parenchymatous atrophy of the cerebellum, *J. nerv. ment. Dis.*, **48**, 273 - 312.

BAKKER, S. P. (1924) Atrophia olivo-ponto-cerebellaris, *Zeit. ges. Neur. Psych.*, **89**, 213 - 244.

VAN BOGAERT, L., and BERTRAND, I. (1929) Une variété d'atrophie olivo-pontine à évolution subaiguë avec troubles démentiels, *Rev. Neurol.*, **1**, 165 - 178.

——, and BORREMAN, P. (1947) Sur une atrophie cérébelleuse corticale avec début de sclerose axiale et atteint des noyaux gris centraux. Troubles mentaux. Lipomatose symetrique, *J. Belge Neurol. Psychiat.*, **47**, 249 - 267.

—— (1947) Sur une atrophie cérébelleuse tardive du type Marie-Foix-Alajouanine héréditaire et familiale avec une atrophie pallidale partielle cliniquement muette, *J. Belge Neurol. Psychiat.*, **47**, 268 - 286.

—— (1946) Aspects cliniques et pathologiques des atrophies pallidales et pallido-Luysiennes progressives, *J. Neurol. Neurosurg. Psychiat.*, **9**, 125 - 157.

BROUWER, B., and BIEMOND, A. (1938) Les affections parenchymatouses du cervelet et leur signification au point de vue de l'anatomie et de la physiologie de cet organe, *J. Belge Neurol. Psychiat.*, **38**, 691 - 757.

BROUWER, B., and SCHLESINGER, F. G. (1947) Carcinoma ovarii and cerebellar degeneration, *Proc. K. Akad. Web. Am.*, **5**, 1329.

—— (1934) Familial olivo-ponto-cerebellar hyperplasia in cats, *Psychiat. Neurol. Bl.*, **38**, 352 - 367.

CARP, E. A. D. E. (1925) Sur la function de la couche des grains du cervalet, *Psych. en Neurol. Bl. Amst.*, **29**, 10 - 20.

COMBETTE (1831) Atr. compl. du cerveau etc. chez une jeune fille morte dans sa 11th année, *J. de Phys. Exp. et path. de Magendie*, 27 - 45.

CORNÉLIUS, R. (1907) Les atrophies croisées du cervelet, *Thèse de Paris, Russel.*

CRITCHLEY, M. (1939) Spastic dysphonia ("Inspiratory speech"), *Brain*, **62**, 96 - 103.

DAVISON, C., and WECHSLER, I. S. (1938) Olivo-ponto-cerebellar atrophy and unilateral involvement of cranial nerve nuclei, *J. nerv. ment. Dis.*, **88**, 569 - 588.

DÉJÉRINE, J., and THOMAS, A. (1900) L'atrophie olivo-ponto-cérébelleuse, *Nouv. Iconogr. Salpêt.*, **13**, 330 - 370.

ESSICK, C. R. (1907) The corpus ponto-bulbare—a hitherto undescribed nuclear mass in the human hind brain, *Am. J. Anat. Balt.*, **7**, 119 - 135.

—— (1909) On the embryology of the corpus ponto-bulbare and its relation to the development of the pons, *Anat. Rec. Phil.*, **3**, 254 - 257.

—— (1912) The development of the nuclei pontis and the nucleus arcuatus in man, *Am. J. Anat.*, **13**, 25 - 54.

FICKLER, A. (1911) Klinische und pathologisch-anatomische Beitrage zu den Erkrankungen des Kleinhirns, *Dtsch. Z. Nervenheilk.*, **41**, 306 - 375.

FINLEY, K. H. (1935) Anat. study in familial olivo-ponto-cerebellar hyperplasia in cats, *Proc. Kon. akad. Web. Amsterdam.*

FRASER, D. (1880) Defect of the cerebellum occurring in a brother and sister, *Glasgow med. J.*, **13**, 199 - 210.

GALLEMAERTS, V., KLEYNTJENS, F., and CLOETENS (1939) Hérédo-ataxic cérébelleuse de Pierre Marie. Evolution en syndrome spastique avec contractions myocloniques, *J. Belge Neurol. Psychiat.*, **39**, 667 - 675.

GREENFIELD, J. G. (1934) Subacute spino-cerebellar degeneration occurring in elderly patients, *Brain*, **57**, 161 - 176.

GUILLAIN, G., BERTRAND, I., ET GUILLAIN, J. (1939) Etude anatomo-clinique d'un cas d'atrophie cérébelluse corticale progressive, *Bull. et mem. Soc. Med. Hôp. de Paris*, **55**, 218 - 229.

——, THÉVENARD, A., ET JONESCO (1928) Un cas de syndrome cérébelleux du type de l'atrophie olivo-ponto-cérébelleuse avec developpement progressif d'un état hypertonique. *Rev. neurol.*, **2**, 890 - 895.

HALL, B., NOAD, K. M., and LATHAM, O. (1941) Familial cortical cerebellar atrophy, *Brain*, **64**, 178.

—— —— —— (1945) *Med. J. Austral.*, **1**, 101 - 108.

HANEL, H., and BIELSCHOWSKY, M. (1914-15) Olivo-cerebellare Atrophie unter dem Bilde des familiären Paramyoclonus, *J. Psychus. neur.*, **21**, 385 - 415.

DE HAENE, A. (1937) Contribution à l'étude clinique et anatomique de l'atrophie cérébelleuse tardive à prédominance corticale, *J. Belge Neurol. Psychiat.*, **37**, 427 - 454.

HASSIN, G. B. (1935) Crossed atrophy of the cerebellum. No clinical symptoms of cerebellar disease during life, *Arch. Neurol psych.*, **35**, 917 - 928.

——, and HARRIS, T. H. (1936) Olivo-ponto-cerebellar atrophy, *Arch. Neurol. psych.*, **35**, 43 - 63.

HOLMES, G. (1907) An attempt to classify cerebellar disease with a note on Marie's Hereditary Cerebellar Ataxia, *Brain*, **30**, 545 - 567.

—— (1907) A form of familial degeneration of the cerebellum, *Brain*, **30**, 466 - 489.

HORNEVALD, G. (1923) De beteckenis der olivo-pontine atrophie voor de kennis van palaeo- en neo-cerebellum, Diss. Inaugr. 17 Feb. Utrecht.

JELGERSMA (1919) Eine Systemerkrankung im Kleinhirn, *Journ. f. Psychol. u Neurol.*, **25**, 42 - 46.

KEILLER, W. (1926) 4 cases of olivo-ponto-cerebellar atrophy giving history of heredity with three autopsies, *Sth. med. J.*, **19**, 518-522.

KENNARD, M. A. (1944) Experimental analysis of the functions of the basal ganglia in monkeys and chimpanzees, *J. neurophysiol.*, **7**, 127 - 148.

LEY, R. A. (1924) Forme atypique d'atrophie cérébelleuse ayant évolué en syndrome rigide, *Arch. intern. med. exp.*, **1**, 277.

LHERMITTE, J. (1922) L'astasie-abasie cérébelleuse par atrophie vermienne chez le vieillard, *Rev. Neurol.*, **1**, 313 - 316.

LEJONNE, P., et LHERMITTE, G. (1907) Atrophie olivo et rubro-cérébelleuse, *Rev. Neurol.*, **17**, 109 - 113.

——, —— (1909) Atrophie olivo-rubro-cérébelleuse essai de classification des atrophies du cervelet. *Nouvelle Iconogr. Salpêtrière*, **22**, 605 - 619.

——, and KLARFIELD, B. (1911) Etude anatomique d'un cas d'atrophie croisée du cervelet, *Rev. neurol.*, **22**, 73 - 74.

LICHTENSTEIN, B. W. (1945) Cerebellar atrophy. 1. An analysis of the various forms and an analytical scheme for their study, *J. Neuropath. exp. Neurol.*, **4**, 379 - 392.

LUQUE, O., and PUCHETA MORCILLO, R. (1945) Atrophia olivo-ponto-cerebelosa, *Rev. argent. Neurol. y psiquiat.*, **10**, 17 - 48.

MAJOR, H. C. (1879) Case of paralytic idiocy with right-sided hemiplegia; epilepsy; atrophy with sclerosis of the left hemisphere of the cerebrum and of the right lobe of the cerebellum, *J. ment. Sci.*, **25**, 161 - 165.

MARIE, P. (1893) Sur l'hérédo-ataxic cérébelleuse, *Semaine med.*, **13**, 444 - 447.

——, FOIX, CH., ET ALAJOUANINE TH. (1922) l'atrophie cérébelleuse tardive à prédominance cortical, *Rev. neurol.*, **2**, 849 - 885, 1082 - 1111.

MARBURG, O., and RIESE, E. (1947) Chronic progressive spino-cerebello-cortical lipodystrophy affecting certain arterial supply areas, *J. Neuropath. exp. Neurol.*, **6**, 61 - 77.

MAAS, O., and SCHERER, H. J. (1933 Zur Klinik und Anatomie eigener seltener Kleinhirnerkrankurgen, *Zeit. ges Neurol. & Psychiat.*, **145**, 420 - 444.

MATHIEU, P., and BERTRAND, I. (1929) Etudes anatomo-cliniques sur les atrophies cérébelleuses. (Prix Charcot), *Rev. Neurol.*, **1**, 712 - 739.

MESSING, Z. (1930) Atrophie olivo-cérébelleuse dans un cas de maladie de Parkinson, *Rev. Neurol.*, **1**, 498 - 499.

VON MONAKOW, C. (1895) Experimentelle und pathologisch-anatomische Untersuchunger über die Haubenregion, den Seh hügel und die Regio subthalamica, *Archi. Psychiat. Nervenk.*, **27**, 1 - 30.

MOTT, F. W., and TREDGOLD, A. F. (1900) Hemiatrophy of the brain, of its results in the cerebellum, medulla and spinal cord, *Brain*, **23**, 239 - 260.

MURRI (1900) Degenerazione cerebellare de intossicazione enterogema, *Riv. crit. de clin. med.*, **1**, 593 - 598, 609 - 616.

NICOLESCO, J. (1936) "Les Atrophies cérébelleuses." Toroutiu-Bucharest.

NOICA, D., NICOLESCO, J., and BANU, E. (1936) Contribution à l'étude de l'atrophie olivo-ponto-cérébelleuse, *Rev. neurol.*, **66**, 285 - 306.

NONNE, M. (1905) Ein weiterer anatomischer Befund bei einem Fall von familiäler Kleinhirnataxia, *Arch. f. Psychiat, Berlin*, **39**, 1225 - 1251.

NOTHNAGEL, VON (1879) Quoted by Déjérine and Thomas.

PARKER, H. L., and KERNOHAN, J. W. (1933) Parenchymatous cortical cerebellar atrophy (chronic atrophy of Purkinje cells), *Brain*, **56**, 191 - 211.

PIERRET, M. (1872) Note sur un cas d'atrophie péripherée du cerveau avec les concom. des olives bulb, *Arch. de Physiol.*, **4**, 765.

RICHTER, R. (1938) A clinicopathological study of parenchymatous cortical cerebellar atrophy, *Trans. Amer. Neur. Ass.*, **64**, 21 - 23.

ROSSI, I. (1907) Atrophie parenchymateuse primitive du cervelet à localisation corticale, *Nouv. Iconogr. Salpêt*, **20**, 66 - 83.

SCHERER, H. J. (1933) Extrapyramidelle störungen bei der olivo-ponto-cerebellaren Atrophie. Ein Beitrag zum Problem der lokalen vorzeitigen Alterns, *Zeit. ges. Neurol. Psychiat.*, **145**, 406 - 419.

SCHROEDER and KIRSCHBAUM, W. (1928) Ueber eigenartige degenerative Erkrankungens der zentral Nervensystems mit vorwiegender Beteiligung des olivo-cerebellaren Systems und Grosshirnrindenveränderungen, *Zeit. ges. Neurol. Psychiat.*, **114**, 681 - 733.

SCHULTZE (1887) Ueber einen Fall von Kleinhirnschwund mit degenerationen im verlängerten Marke und im Ruckenmark, *Arch. f. path. Anat. Berlin*, **108**, 331 - 343.

SCHUSTER, P. (1924) Die im hoheren Lebensalter vorkommenden Kleinhirnerkrankungen nebst Bemerkungen über dem cerebellaren Wackeltremor, *Zeit. ges. Neurol. Psychiat.*, **91**, 531 - 550.

SCHUT, J. W. (1946) Olivoponto-cerebellar atrophy in a cat, *J. neuropath. exp. neur.*, **5**, 77 - 81.

SMITH, G. ELLIOT (1903) The morphology of the human cerebellum, *Rev. neurol. psychiat.*, **1**, 629 - 639.

VON STAUFFENBERG (1918) Zur Kenntnis des extrapyramidalen motorischen Systems und Mitteilung eines Falles von Atrophia olivo-ponto cerebellares, *Zeit. ges. Neurol. Psychiat.*, **39**.

THOMAS, ANDRÉ (1905) Atrophie lamellaire des cellules de Purkinje, *Rev. neurol.*, **13**, 917 - 924.

—— (1897) Le Cervelet, Paris.

——, and CORNÉLIUS, R. (1907) Un cas d'atrophie croisée du cervelet, *Rev. neurol.*, **15**, 197 - 205.

TITECA, J., and VAN BOGAERT, L. (1946) Heredo-degenerative hemiballismus. A contribution to the question of primary atrophy of the corpus luysii, *Brain*, **69**, 251 - 263.

WEBER, F. P., and GREENFIELD, J. G. (1942) Cerebello-olivary degeneration: an example of heredo-familial incidence, *Brain*, **65**, 220 - 231.

WILSON, S. A. KINNIER (1940) Neurology, Arnold, London, **11**, 964 - 965.

WINKLER, C. (1923) A case of olivo-pontine cerebellar atrophy and our conceptions of neo- and palaeo-cerebellum, *Schweiz. Arch. Neurol. Psychiat.*, **13**, 684-702.

SUBACUTE INCLUSION ENCEPHALITIS
(Dawson type)

BY

W. RUSSELL BRAIN, J. G. GREENFIELD AND DOROTHY S. RUSSELL

ATTENTION was drawn by us in 1943 (Brain, Greenfield and Russell, 1943) to a form of subacute ingravescent encephalitis which had been described by Dawson in the United States in 1933 and 1934. At that time we reported briefly on the examination of two cases which had occurred in the London district during the previous three years. Since that time we have had the opportunity of making a post-mortem examination of two further cases and in recording these take the opportunity of giving a fuller description of the two cases we had previously recorded, and of discussing the position of the disease in relation to other forms of encephalitis.

INCLUSION ENCEPHALITIS

Case 1.—D. B., male, aged 4 years and 4 months, was admitted to the Queen's Hospital for Children, Hackney Road, on September 4, 1939, under the care of Dr. Alice King to whom we are indebted for the clinical notes.

Clinical history.—Six or seven weeks before admission the child was noticed to limp with his right leg. Two weeks before admission there was weakness of the upper limbs, and incontinence of urine. Loss of power in all four limbs developed one to two weeks and fæcal incontinence three days before admission. No changes in mentality or behaviour had been noted.

On examination the child was unable to stand or sit up. Speech was indistinct. Periods of irritability alternated with lethargy. No defect was found in any of the cranial nerves. There was no wasting. On the motor side there was flaccidity and diminished power in the arms; the legs were spastic. All reflexes were present, being brisk in the legs. The plantar reflexes were flexor. No sensory changes could be elicited owing to lack of co-operation. *Lumbar puncture* on the day after admission yielded clear colourless cerebrospinal fluid under a pressure of 120 mm. and containing 10 mg. per cent. of protein, 0·7 per cent. of chlorides and 1 lymphocyte per 2 c.mm. Cultures of the fluid were negative.

Progress.—During the period in hospital there was an occasional rise in temperature of 99° and 100° F. On September 6, ataxy of both arms was noted and a slight internal strabismus of the left eye. September 7: There was right wrist-drop. September 19: There appeared to be slight general improvement and he could lift his head off the pillow. On September 30, however, swallowing became difficult and he was apparently blind and spastic with a bilateral extensor plantar response.

Death took place on October 6, 1939, eleven weeks after the onset of the illness; a rise of temperature to 106° F. was recorded on this day.

A necropsy was performed twenty-four hours later by the late Dr. Elizabeth

O'Flynn. Examination showed the body of a well-nourished boy. There were emphysema of the lungs, slight fatty degeneration of the liver and a cortical scar in the right kidney. No further abnormality in chest and abdomen was found.

Brain (weight 1,441 grammes).—The cerebral hemispheres were symmetrical and all convolutions full. The meninges were moist. On horizontal section through one hemisphere the white matter was homogeneous and felt somewhat rubbery. The grey matter and ventricles appeared normal.

The spinal cord was not removed.

No additional macroscopic changes were found on further section of the brain when hardened in formaldehyde.

Microscopic examination.—Blocks from both Rolandic areas, left frontal cortex, right hippocampus, right occipital (area striata), left occipital (convexity), right basal ganglia, mid-brain through anterior corpora quadrigemina, pons through fifth roots, upper medulla oblongata, dentate nucleus, cerebellar cortex and the choroid plexus from a lateral ventricle were embedded in paraffin. Sections were stained with Ehrlich's hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, and with phosphotungstic-acid hæmatoxylin. Some sections from the cerebral cortex were also stained for Nissl substance and by Loyez' hæmatoxylin for myelin.

Frozen sections from the left Rolandic and occipital cortex were stained by silver carbonate for astrocytes and microglia, a few of the latter sections being counterstained with Sudan III

Over the *cerebral cortex* the leptomeninges were slightly thickened by fibrosis, and sparsely infiltrated with small groups of lymphocytes and plasma cells which tended to lie near blood-vessels in the depths of the sulci. A similar, more abundant infiltration was present in the adventitial sheaths of the perforating vessels, and conspicuous cuffs of the cells were often found in the sheaths towards the junction of the grey and white matter. Both veins and arterioles were affected.

A large proportion of the pyramidal cells exhibited stages of chromatolysis leading to necrosis. Such changes were often associated with the presence within the nucleus, and sometimes within the cytoplasm also, of oval or round inclusions or eosinophil material. The intranuclear inclusion was usually solitary, but occasionally two or more were present. It generally lay at the centre of the nucleus while the nucleolus and nucleoplasm were displaced to the periphery, being separated from the inclusion body by a clear halo. In the earlier stages the inclusion was about the same size as the nucleolus (fig. 1) but later it increased until almost the whole of the nucleus was occupied. It was then outlined by a dense ring of chromatin applied to the nuclear membrane (fig. 3). With high magnifications the inclusion appeared finely granular but showed no further structural details. It showed no affinity for silver carbonate, but was pale bluish-green in Nissl preparations and faint purple with phosphotungstic-acid hæmatoxylin. It had a variable affinity for phloxin in sections stained by Lendrum's phloxin-tartrazine method.

The cytoplasmic eosinophil inclusions were of irregular shape, accommodating themselves to the confines of the cell. Occasionally they occupied the adjacent axis cylinder. They appeared hyaline, non-granular and deep purple with phosphotungstic-acid hæmatoxylin, though they took the same tint as the intranuclear inclusions in Nissl preparations. Their affinity for silver carbonate was not determined. They were strongly phloxinophil in sections stained by Lendrum's phloxin-tartrazine method.

The degeneration of the pyramidal cells was associated with a conspicuous proliferation of the microglial cells, many of which were rod-shaped (figs. 1 and 2). No inclusion bodies were identified in these cells. A few, however, were present

in the nuclei of the oligodendroglial cells which showed, in general, advanced stages of acute swelling.

In the deeper layers of the cortex the astrocytes had undergone slight proliferation and this was more intense in the immediately subjacent white matter. No inclusion bodies were found within these cells. Although individual axis cylinders and their sheaths had frequently undergone degeneration there were no patches or zones of demyelination in the centrum ovale. Sparsely distributed fat-granule cells, and cuffs of similar cells in the Virchow-Robin spaces of blood-vessels penetrating the white matter, provided evidence of the more diffuse character of the degeneration.

Distribution of changes in cerebral cortex.—Although all parts of the cerebral hemispheres examined were affected, the distribution of inclusion bodies and severity of the changes was uneven. The cortex of the occipital and motor areas was more affected than the hippocampal and frontal regions.

In the *basal ganglia* perivascular cuffing was of moderate severity and there was considerable generalized degeneration of the neurones. Only one intranuclear inclusion was found occupying a ganglion cell in the caudate nucleus. Slight gliosis was present in the thalamus.

In the *mid-brain, pons* and *medulla oblongata* meningitis was absent but there was focal cuffing of the perforating vessels associated with degeneration of neurones. A few intranuclear inclusion bodies were found in the olives only. The neurones of the substantia nigra showed severe chromatolysis without inclusion bodies. A few small lymphocytes were present in the nervous tissues here and in the nuclei of the third nerve.

No histological changes were present in the *cerebellum* apart from severe chromatolysis in the Purkinje cells, many of which had disappeared, and in the dentate nucleus.

There was severe degeneration, with pyknosis and karyorrhexis, of the epithelium of the choroid plexus in the lateral ventricle. The stroma appeared normal. No inclusion bodies were identified.

Case 2.—*History.*—D. H., male, aged 11 years. On July 7, 1942, he received his first inoculation of 0·2 c.c. of alum-precipitated toxoid against diphtheria. Three or four days later his parents noticed that he had become forgetful and when sent on an errand could not remember what to do unless it was written down. He became a messy eater and lolled at the table and was nervous when on his bicycle. These symptoms continued until August 11 when he had his second inoculation of 0·5 c.c. of A.P.T. On August 13 while getting into bed he fell out on to his head, cutting the right side of his forehead which required to be stitched. On August 15 he was noticed to be unsteady in walking and the next day had to hold on to things to prevent himself from falling. He could not see his dominoes nor find the electric light switch. On August 17 he was admitted to the Connaught Hospital, Walthamstow, under the care of Dr. Kenneth Perry and on August 31 he was transferred to Chase Farm Hospital, Enfield. During his stay in the Connaught Hospital his speech became increasingly indistinct and he became incontinent.

Condition on September 4, 1942.—Conscious but unco-operative. Speech slurred and almost unintelligible. Optic discs normal. Visual fields appear full on confrontation. Pupils moderately dilated, reacting briskly to light and acccommodation. Ocular movements full; slight bilateral ptosis. Moderate trismus. Bilateral facial spasm producing a risus sardonicus. Weakness of voluntary movement of left side of face. Soft palate and tongue normal. There were intermittent attacks of clonic spasms of the flexors of the right upper and lower limbs, synchronous in both. Between these attacks voluntary movement of these limbs was fairly strong. A grasp reflex was obtainable from the right hand. There was spastic weakness of

the left upper and lower limbs with an intermittent tremor of the left upper limb. The tendon reflexes were exaggerated but equal on the two sides in both upper and lower limbs. The right plantar reflex was flexor and the left extensor. Pin-prick was felt on both sides of the body, possibly more keenly on the right than on the left. No other form of sensibility could be tested. Cervical rigidity and Kernig's sign absent. Temperature 99°, pulse 72, respirations 18.

September 8, 1942, lumbar punctured: C.S.F. pressure 100 mm. 4 c.c. slightly blood-stained fluid. Cells 3 per c.mm. all lymphocytes. Red cells—1,000 per c.mm. Globulin negative. Total protein 30 mg. per cent. Chloride 0·72 per cent. Culture sterile.

Blood W.R. negative. Kahn negative. Red blood count normal. Total and differential white blood count normal.

Subsequent history.—By September 7 he was completely unconscious and nasal feeding was begun. In both fundi to the temporal side of the optic disc a round white patch of choroidoretinitis about double the diameter of the disc was seen. Both upper limbs were now spastic in flexion and both lower limbs in extension, both plantar reflexes being extensor. Towards the end of the second week in September the temperature rose and at the end of the third week reached 103·5°. It remained, with slight variations at about 102°, and the pulse-rate about 120 until October 13 when he died, three months after the onset of his illness. During the last five weeks of his life his nervous condition resembled that of decortication.

On September 15 he was given 15,000 units of diphtheria antitoxin and on September 16 a further 10,000 units and 10,000 units were given on September 22, 23, 24, 25 and 26 without any apparent result. On September 30, October 1 and 2, 21 grammes of sulphapyridine were given, also without result.

A post-mortem examination was made on 14.10.42, twenty-one hours after death.

The liver, spleen, kidneys and suprarenal bodies appeared normal microscopically.

The lungs showed patchy collapse of both lower lobes, with small foci up to half an inch in diameter of bronchopneumonia.

No intranuclear inclusions or foci of necrosis were found in the *abdominal organs.*

Apart from unusual firmness the *brain* appeared quite normal. There was no congestion of the cortex or opacity of the meninges.

Pieces were taken for section from the frontal pole, motor, hippocampal and inferior temporal cortex, occipital cortex including the striate area, the basal ganglia, mid-brain, pons, medulla, cerebellum and spinal cord (sixth, seventh and eighth cervical, first and sixth thoracic and second lumbar).

Definite lesions of encephalitis were seen in all parts examined except the cerebellum and the lower thoracic and lumbar levels of the spinal cord. These consisted of degeneration of neurons, many of which in all affected areas contained intranuclear and cytoplasmic inclusion bodies; microglial increase with accumulation of these cells in clusters in the medulla and spinal cord (glial-star formation); perivascular lymphocytic infiltration and astrocytic hyperplasia (neuroglial sclerosis). These reactions and degenerations varied in degree and in proportion to one another in different areas examined, probably according to the age of the process in that area. Neuronal degeneration and neuroglial sclerosis preponderated in the cerebral cortex, microglial proliferation and lymphocytic infiltration in the cervical cord, but all four types of change were seen in greater or less degree in all the affected regions.

A more detailed description of the appearances in each area will indicate these variations.

Motor cortex.—Here there was a general loss of nerve cells and those that remained had shrunken cell bodies so that it was impossible to distinguish the cortical layers. A few Betz cells were present. Some looked almost normal;

others showed central chromatolysis or irregular shrinkage with loss of Nissl granules. None of those seen had intranuclear inclusion bodies. The smaller pyramidal cells were widely affected, many having disappeared, and all having a very shrunken cell body and a hyperchromic nucleus. A considerable number contained intranuclear inclusion bodies, and the cytoplasm of these cells was always very shrunken or ragged and usually showed eosinophilic degeneration. All the astrocytes had large cell bodies, passing off into processes which were readily seen in paraffin sections stained with hæmatoxylin and eosin, but only a few of the thicker processes, especially those going to the blood-vessels (vascular foot processes), contained neuroglial fibres stainable by phosphotungstic acid hæmatoxylin. Paired astrocytes indicating multiplication were numerous.

There was great overgrowth of neuroglial fibres both in the subpial zone and in the deepest layer of the cortex and the neighbouring white matter. There was also enlargement both of the nuclei and processes of the microglial cells, and a few of these cells had a rounded, rather foamy cell body. A few vessels were ringed by a single layer of lymphocytes within the perivascular sheath, but this was not very prominent in the cerebral cortex.

In some areas, more in the superficial cortex than in that bordering the sulci, most of the nerve cells had disappeared, and astrocytes were more numerous than neurons. In the underlying white matter all the astrocytes had swollen cell bodies giving rise to fine fibrous processes, and there was a considerable excess of neuroglial fibres.

Prefrontal cortex.—Conditions here were similar to those in the motor cortex, with even more destruction of neurons and more gliosis and increase in rod cells and other microglial forms.

Hippocampal cortex.—Here there was an almost complete destruction of the layer of pyramidal cells in the zone lying nearest to the ventricle; elsewhere it was fairly well preserved. In the area of maximal destruction almost every one of the few remaining neurons contained an intranuclear inclusion body, and showed severe degeneration of the cell body. The fascia dentata was only slightly affected. There was heavy gliosis with swollen astrocytes in the affected zone of pyramidal cells. The neighbouring part of the hippocampal gyrus showed a degree of neuronal degeneration comparable with that in the motor cortex, with very many intranuclear inclusion bodies.

On the inferior surface of the *temporal lobe* near its external border there were areas in which the majority of the nerve cells contained intranuclear inclusion bodies and were severely degenerated. Slight perivascular lymphocytic infiltration was seen in this region round the cortical veins.

Occipital cortex.—Here there was little destruction of neurons and the general architecture and cortical layers were little disturbed. No marked neuroglial or microglial proliferation was present here, although in the underlying white matter the astrocytes had rather swollen cell bodies and some increase of fibres. In one sulcus there was considerable lymphocytic infiltration of the pia-arachnoid. However, with higher magnification many nerve cells were found to be in various stages of degeneration and many intranuclear inclusion bodies were seen in them.

Thalamus.—The whole nucleus was fairly severely involved but in a somewhat patchy manner. In the most severely affected areas most of the nerve cells had disappeared. A few were recognizable as such, and presented various degrees of chromatolytic degeneration, many having their nuclei flattened under the cell membrane, others were only recognizable as nuclei containing inclusion bodies with a shred of cytoplasm round them. There was considerable gliosis and increase in number and size of microglial nuclei. There was also considerable lymphocytic cuffing round many of the veins. In places the tissue was vacuolated, even in celloidin sections.

Caudate nucleus and putamen.—These nuclei were only slightly affected but showed slight gliosis with the presence of a number of neuroglial fibres in all areas. These were chiefly vascular processes but several others were seen. Occasional nerve cells contained intranuclear inclusions but most were normal. Slight lymphocytic cuffing was seen round a few veins.

Globus pallidus.—This was in general fairly normal, but a considerable proportion of neurons appeared degenerated and contained intranuclear inclusions. Owing to the absence of small nerve cells in this nucleus it was possible to establish with certainty that occasional oligodendroglial nuclei contained inclusion bodies. Occasional plasma cells were seen here close to the wall of capillary vessels. There was slight swelling of the bodies of the astrocytes.

Mid-brain.—Both in the substantia nigra and the nucleus ruber there was some excess of microglial nuclei and numerous vessels in the latter situation showed perivascular lymphocytic infiltration. A few nerve cells were degenerated and contained intranuclear inclusion bodies. The cells of the substantia nigra thus affected had begun to shed their granules which were loosely grouped round the cytoplasm of the cell.

Pons.—Here also there was gliosis and increase of microglial cells in the ventral portion, especially round the nuclei pontis. The astrocytes were all swollen and their neuroglial fibres more numerous and rather thicker than normal, producing a gliosis in the ventral part of the pons. Degenerated nerve cells containing intranuclear inclusions were more numerous there than in the mid-brain nuclei, and occasional nuclei, indistinguishable from oligodendroglial nuclei, also contained small inclusion bodies.

Medulla.—A considerable number of degenerated nerve cells with intranuclear inclusions were found in the inferior olive. One contained two inclusion bodies. In the lower medulla the nuclei gracilis and cuneatus also contained many degenerated neurons with intranuclear inclusions.

Spinal cord.—As has been stated the lower thoracic and lumbar segments examined showed no abnormality. In the cervical segments and first thoracic segment, however, a few nerve cells both in the ventral and dorsal horns were degenerated and contained intranuclear inclusions. Several of the large ventral horn cells contained more than one inclusion body; as many as six were seen in one cell, and in others the inclusion body was lobulated as though it had resulted from the fusion of several smaller bodies (figs. 5 to 8). Occasional degenerated cells were surrounded or overlaid by microglial cells, a condition of early neuronophagy.

The cytoplasm of many of the affected ventral horn cells contained a few granules which stained with eosin a bright red colour, almost as bright as that of red blood cells. The larger of these usually lay in the periphery of the cell. With phosphotungstic acid hæmatoxylin these granules stained pink, but many other granules and curled thread-like structures were also seen, chiefly towards the centre of the cytoplasm, which took a deep purple colour with this stain. Granules of the latter kind are seen in many forms of neuronal degeneration, but they were specially abundant in this case. The cells with these purple-staining cytoplasmic granules were usually found to contain one or more intranuclear inclusion bodies. Although more easily seen in the large ventral horn cells, intranuclear inclusion bodies were present in a larger proportion of the neurons of the dorsal horns (figs. 9 and 10).

Quite intense perivascular lymphocytic infiltration was present in several of the lower cervical segments of the cord. The larger veins in the grey matter and grey commissure were chiefly involved. A few glial stars composed chiefly of microglial cells were also present in the grey matter in these segments.

Pieces of fresh tissue were sent in buffered glycerine saline to the late Professor J. McIntosh of the Bland-Sutton Institute, who with Dr. F. R. Selbie injected them

intracerebrally into mice and rabbits and inoculated them also on to the scarified cornea of rabbits, without result.

Case 3.—G. B., female, aged 10 years. Reg. No. 40917/1945 (London Hospital).

Clinical history.—At the age of 2 she had measles and "kidney trouble"; at 3 years two attacks of pneumonia; at 5 years bilateral otitis media. One month before the onset of her terminal illness there had been recurrence of earache, but after three days she was able to return to school. Apart from these illnesses she seems to have been a normal child until nine weeks before death when her work at school became slovenly. This was followed by rapid mental deterioration; she soon became unable to dress herself and her speech was unintelligible. There was no complaint of headache. A month later she was brought home to London from the country district to which she had been evacuated during the war; she then did not recognize her mother.

On admission to the London Hospital under Dr. Henry Wilson, four weeks before death, she appeared well nourished. She was never obstreperous but was unco-operative, and would sit silent and morose, and slept for long periods.

On examination.—The fundi showed pallor of the discs, but were otherwise normal. Pupils: sluggish reaction to light. No abnormality in any of the cranial nerves. No nystagmus. Limbs: resistance to passive movement. Occasional involuntary twitchings. Tendon reflexes normal in upper limbs; increased in lower limbs. Flexor plantar responses.

Blood: slight leucocytosis. Wassermann reaction negative.

Lumbar puncture yielded cerebrospinal fluid under increased pressure, with normal protein and no excess of cells. Wassermann reaction negative. Lange: paretic type of curve. Urine: a trace of albumen present.

Progress.—Temperature swinging between 97° and 103°. She steadily deteriorated and, two weeks before death, became unable to feed herself or to recognize anybody. She lapsed into a state of decerebrate rigidity with spasticity of the limbs and finally periodic convulsive attacks which affected the whole body. At this time she showed a divergent squint; the pupils were unequal and reacted poorly to light, especially the left. Death took place from respiratory failure.

Summary of necropsy (P.M. 6/1945).—Performed forty hours after death.

Lateral sinus thrombosis. Bronchopneumonia. "Inclusion encephalitis."

Bronchopneumonia, with occasionally confluent areas of consolidation, in lower lobe of right lung. Emphysema of remainder of lungs. Slight parenchymatous degeneration of myocardium. Very slight general atheroma. Considerable fatty change, microscopically most marked in periportal areas, in the liver. Severe parenchymatous degeneration with, microscopically, hyaline-droplet degeneration and rarely fatty degeneration in occasional first convoluted tubules, and hyaline casts in collecting tubules of kidneys. Slight congestion and no microscopic alteration in spleen. Normal pancreas, suprarenal glands, thymus and pituitary gland. No macroscopic or microscopic changes in stomach and intestines apart from post-mortem alterations. Absence (old operation) of tonsils. No abnormality in middle ears, mastoid cells, accessory air sinuses and nasal mucosa. Marked convolutional impressions on inner table of skull. Ante-mortem thrombus lightly adherent to, and filling left lateral sinus. A greatly wasted, well-developed girl.

Weights.—Body, 14·88 kg.; length, 1·3 m.; heart, 99 grammes; liver, 483 grammes; kidneys, 92 grammes; suprarenals, 7·6 grammes; spleen, 35 grammes; pituitary, 0·3 gramme; thyroid, 3·05 grammes; thymus, 3·1 grammes; pancreas, 27·1 grammes; ovaries, 1·5 grammes.

Examination of brain.—With aseptic precautions portions of the left frontal and right occipital cortex, the left basal ganglia, upper pons, and cerebellum were removed for experimental transmission to laboratory animals. The rest of the brain was fixed in formaldehyde. On section there was diffuse engorgement and

numerous pin-point hæmorrhages formed an ill-defined zone in the subcortical white matter in many parts of the cerebrum. In these areas the white matter often showed a diffuse yellowish-grey discoloration but without obvious alteration in texture. In a few areas, however, there was obvious friable softening of the white matter, namely in the left post-central gyrus, the left occipital and occipito-parietal convexity extending medially to the parasagittal region, and the medial surface to the calcarine fissure. The right occipital convexity was similarly affected in the area from which bits had been removed for animal-transmission. No naked eye changes were found in the basal ganglia, brain-stem or spinal cord.

Microscopic examination.—Blocks from the left frontal convexity, inferior surface of right frontal lobe including the olfactory tract, left temporal region including Ammon's horn, right Rolandic cortex, right occipital cortex, left post-central cortex; basal ganglia on both sides, mid-brain, pons, cerebellum, medulla oblongata, posterior part of left eyeball and representative levels of the cord, and the left ventricular choroid plexus were embedded in paraffin. The posterior root ganglion of the twelfth thoracic segment on the right, a Gasserian ganglion, the semilunar ganglion and right sympathetic chain were similarly treated. Frozen sections were prepared and stained by a variety of silver techniques from the left frontal and right occipital regions, the blocks being adjacent to those taken for paraffin sections. The stains used were the same as in Case I.

The greatest changes were in the cerebral cortex and the immediately subjacent white matter. All parts of the cortex were affected, but the changes varied considerably in intensity in different areas. The most severe were in the right occipital lobe and left post-central region. Both here and elsewhere meningitis was slight and was confined to a sparse infiltration with a mixture of small lymphocytes, large mononuclear cells and occasional neutrophil leucocytes. There was slight cuffing of a moderate number of the perforating vessels in the occipital lobe with similar cells, predominantly lymphocytes. Elsewhere cuffing was very scanty or absent. The most conspicuous changes were in the pyramidal cells, a variable proportion of which were affected in the same manner as in Case I. In general the cytoplasmic and intranuclear inclusion bodies were more numerous in the present case; in some areas, for example the occipital cortex, almost every neurone was so affected. The microglial response, with the production of transitional forms and rod-cells was proportionate to the neuronal degeneration and destruction. In the subcortical white matter there was correspondingly a variable loss of axis-cylinders associated with aggregates of foam-cells which, in silver preparations, were demonstrated as rounded-up microglial cells laden with sudanophil lipoid. In situations where the bodies of the neurones were most heavily occupied by inclusions the subcortical white matter, as noted macroscopically, was obviously softened. But in Loyez preparations the demyelination in such areas was poorly defined and incomplete. Gliosis of the subcortical white matter, and of the deeper layers of the cortex, was usually conspicuous. Fresh hæmorrhages, which tended to be perivascular, were present in the white matter in some areas. No inclusion bodies were identified with certainty in the neuroglia, ependyma or choroid-plexus epithelium.

In the *basal ganglia* there was slight perivascular cuffing in the corpus striatum, and a very few intranuclear inclusion bodies were present in neurones in the lenticular nuclei and thalamus.

The *mid-brain* showed uneven chromatolysis of the neurones in the substantia nigra, with one doubtful intranuclear inclusion body, and slight cuffing of an adjacent perforating vessel. There was no meningitis over the *cerebellum*. Chromatolysis affected many of the Purkinje cells and these were missing in some areas, while the Bergmann cells had undergone focal proliferation. No inclusion bodies were present. Chromatolysis was present in the *nuclei pontis* and a few inclusion bodies were identified within these neurones. Two also were found in

nuclei that appeared to belong to oligodendroglial cells. There was slight cuffing of the perforating vessels in the ventral half of the pons, but no evidence of meningitis. The neurons of the inferior olives showed considerable pyknosis and there was slight chromatolysis in the tegmental nuclei of the *medulla oblongata*. In this region there was some microglial proliferation, but no inclusion bodies were found at this level.

The seventh cervical, third and ninth thoracic and second lumbar segments of the *spinal cord* showed no histological abnormality.

In the twelfth thoracic right *posterior root ganglion* there was chromatolysis and some ganglion cells were shrunken and deeply hæmatoxyphil. No inclusion bodies were present.

The Gasserian ganglion and semilunar ganglion appeared normal.

Portions of the right sympathetic chain showed chromatolysis of some ganglion cells, and one was largely replaced by polymorphonuclear leucocytes. No inclusion bodies were found.

Inclusion bodies in other tissues.—A special search was made for these in sections of the nasal mucosa, pharynx, stomach, small intestine, liver, pancreas, and lung with negative results.

Experimental transmission to animals.—Samples of brain tissue, as already indicated, were sent to three different laboratories. Intracerebral inoculations were made into rabbits, guinea-pigs, mice and two hamsters with negative results.

Case 4.—M. J. (male) was seen in the Out-Patient Department of the National Hospital on April 25, 1947, by Dr. Macdonald Critchley to whom he had been sent from Charing Cross Hospital by Dr. Doyne Bell for an opinion. He was at that time 5 years and 11 months old. The boy's history was that he had developed normally till September 1946 when he had a febrile illness diagnosed as acute rheumatism. In January 1947 he began to make unsteady movements of the hands and head, he tended to stumble and drop his cup out of his hands. Incontinence of urine appeared at this time and persisted. By March he was much worse, and was having attacks with a frequency of about one a minute in which he fell forwards with an apparent relaxation of the skeletal muscles for a fraction of a second, but did not actually fall. His speech also deteriorated. He had vomited several times during the week previous to his visit to the National Hospital. Paresis of the facial musculature on the right side had appeared in March 1947, and for about four months there had been incontinence of urine.

While in Charing Cross Hospital in March a lumbar puncture had been performed, the fluid being found to be quite normal. (The Lange reaction was not performed on the fluid.) A blood-count and X-ray examinations of the head and chest also gave normal results.

When seen in the National Hospital he lay on his back with his legs flexed, making large flexion athetotic movements more with the right than with the left leg. There were also constant myoclonic jerkings of all his limbs, sometimes small in amplitude and at other times coarser and more violent. There appeared to be transitory losses of consciousness. He was apathetic, and showed little if any voluntary movement except feebly to clutch his teddy bear when it was put in his arms. He could follow a light or the noise of jangling keys. When anything approached his lips he was apt to open his mouth and if the object was brought into contact with it to suck or bite at it. The nurse had noticed that when he was fed with a spoon even if his mouth was already full he would open his lips at the sight of food. The pupils reacted to light and accommodation. His eyes followed moving objects without evident hesitation; there was no nystagmus. There was evident weakness of the right lower face. He ate extremely slowly but did not choke. He did not speak but occasionally made a slight whining noise, as for example when he was tested by pin-prick, which he resented on all parts of the

body. He withdrew his feet when they were pinched. The tendon-jerks were all present, the ankle-jerks being very feeble. The abdominal reflexes were absent and the plantars gave a flexor type of response. The examination showed a general picture of progressive dementia, with apathy, speechlessness, paralysis and rigidity and the diagnosis rested between a post-encephalitic state and a form of progressive cerebral degeneration. An electro-encephalographic examination was made a week later by Dr. Denis Williams who reported "A grossly abnormal E.E.G. Episodes of high-voltage spikes showing a sharp phase reversal were present in the posterior parietal regions. They were synchronous with the myoclonic jerks. Transverse leads showed persistent phase reversal in the left hemisphere and all the evidence pointed to a severe biparietal abnormality more evident on the left side."

He returned to Dr. Doyne Bell's ward in Charing Cross Hospital and during the subsequent weeks his condition deteriorated very rapidly. He went home in May, but was sent into Hillingdon County Hospital on June 3, 1947. On examination there the patient was lightly comatose responding to the stimulus of noise by convulsive movements of the right hand and arm and resisting attempts to open the mouth. There was generalized spasticity and the jerks were equal on the two sides, there was a bilateral extensor plantar response and ankle clonus was present on both sides. He deteriorated steadily and developed bronchopneumonia from which he died on July 7 having been ill for about six months.

We are greatly indebted to Dr. Herbert Rogers for sending us notes of his post-mortem examination and half the brain.

A post-mortem examination was carried out by Dr. Rogers on July 8, fourteen hours after death.

External appearance.—An emaciated boy. Bedsore over sacrum.

Internal examination.—Head: Scalp and skull are normal.

Brain: The pial veins are congested. No evidence of meningitis. The left half was sectioned through the basal ganglia; the small vessels are unduly prominent in the basal ganglia. No other visible abnormality.

Mouth: Tongue normal. Tonsils somewhat enlarged.

Thyroid: Normal appearances.

Chest: No fluid exudates or adhesions are present. Thymic tissue is small in amount.

Lungs: Larynx normal. Trachea and larger bronchi normal. Both lungs appear to be normal. No consolidation and no evidence of tuberculosis. No enlargement of mediastinal or hilar glands.

Heart: Pericardium healthy. Heart of normal size. Myocardium healthy. All valves healthy. Coronary vessels and aorta normal.

Liver: Normal size. No visible lesions. Gall-bladder and ducts normal.

Pancreas: Appears to be normal.

Adrenals: Small, but normal.

Spleen: Normal appearance.

Kidneys: Normal size. Smooth surfaces. Slightly toxic appearance of cortical zones. Pelvis, ureters and bladder normal.

Œsophagus: Normal.

Stomach: Normal size. There is a small submucous nodule near the pylorus which may be an adenomyoma or some similar tumour.

Intestine: Normal throughout. Peritoneum healthy.

The right cerebral hemisphere, with the right half of the mid-brain, pons and cerebellum were received from Hillingdon County Hospital. There was definite thickening and opacity of the pia-arachnoid over the fronto-parietal region of the convexity of the cerebrum, with some widening of sulci. The hemisphere was firm, but showed no macroscopic abnormality on section.

Large pieces of cortex measuring 4 cm. in diameter were taken from the frontal

and occipital poles, from the pre- and post-central regions including the corpus callosum about its central part, and from the temporal lobe at right angles to the hippocampus. Horizontal sections were also taken from the basal ganglia at two levels and from several levels of the mid-brain and pons. The cerebellar hemisphere was cut in a sagittal plane through the nucleus dentatus. These pieces were embedded in celloidin and stained by Ehrlich's hæmatoxylin with eosin, iron hæmatoxylin with van Gieson's counterstain, Mallory's phosphotunstic acid hæmatoxylin, Loyez stain for myelin, Heidenhain's azan and thionin blue for Nissl granules. Pieces of frontal and central cortex were also cut frozen, and stained by Scharlach R. with Ehrlich's hæmatoxylin, Cajal's gold sublimate for astrocytes, and the Weil Davenport method for microglia. Paraffin sections of frontal cortex and pulvinar of thalamus were also stained by Lendrum's method for intracellular inclusions.

These sections showed the same general appearances as were seen in the previous three cases. In spite of the longer duration of the disease the degree of gliosis and of destruction of cortical neurons was very similar to that in Case 2. There was, however, rather more microglial hyperplasia with formation of rod cells which in places was very striking and the perivascular infiltration, in this case predominantly with plasma cells, was more prominent both in the grey and white matter. Under the most affected areas of cortex there was considerable gliosis of the white matter, with the formation of swollen-bodied astrocytes and considerable increase in number of microglia. Swollen myelin sheaths, a few of which contained one or more myelophages, were seen in these areas.

While the inflammatory process was diffuse and some degree of it was seen in most of the areas examined, it varied greatly from one area to another without obvious reason. In the *frontal pole* it was greater on the convexity than on the mesial surface. The *precentral gyrus* was severely affected. Here only an occasional Betz cell was recognizable, but in the fifth layer there was a number of large cells with a rounded hyaline highly refractile cell body and an eccentric nucleus which in every case contained an inclusion body. These appeared to represent the remains of Betz cells. The significance of this hyaline change will be discussed later. In a few, short thick processes of similar hyalinized appearance ran out a short distance from the cell body. Here and in other severely affected parts of the cortex it was difficult to recognize the layers owing to loss and degeneration of neurons and proliferation of astrocytes and microglia. Two or four closely set astrocytic nuclei were often seen, and there was great hypertrophy of the neuroglial processes, but except in those running to the larger vessels there was little tendency to the formation of Ranvier-Weigert fibres. Fibrous gliosis was, however, well developed in the molecular layer and at the junction of cortex and white matter.

The number of intranuclear inclusion bodies also varied greatly from place to place. In the less affected areas they were scanty, although degenerated neurons were not infrequent. In the more affected areas of the frontal lobe they were numerous, four or five cells containing inclusion bodies of varying size being seen in most high power fields. In the *calcarine cortex*, which was comparatively slightly damaged, inclusion bodies were not difficult to find in the larger neurons, some filling the nucleus completely, others being quite small, with a diameter about a quarter of that of the nucleus. In the occipital as in the frontal lobe the outer or convex surface was more severely affected than the mesial cortex.

The *temporal cortex* also was only slightly damaged. In the *hippocampus* there was slight diffuse fibrous gliosis with an occasional glial star in the pyramidal layer. In Sommer's sector a few neurons were degenerated and undergoing neuronophagy. Some of these contained inclusion bodies.

In the *basal ganglia* the large neurons of the caudate nucleus and putamen were rather shrunken with a granular cytoplasm, but no inclusion bodies were seen in them. There was slight fibrous gliosis in these nuclei. The globus pallidus showed

little alteration except a slight excess of microglia and swelling of the astrocytic nuclei, without any formation of fibres in their processes.

The *thalamus* was affected in an irregular manner, but everywhere the gliosis and microglial overgrowth tended to be greater than the loss or degeneration of neurons, most of which were fairly normal. However, in the pulvinar and dorsal nucleus some neurons were reduced to the hyaline conditions seen in the Betz cells, and others consisted of a mass of granules staining purple with Mallory's phosphotungstic acid hæmatoxylin, and their nucleus contained an inclusion body. In the *corpora mamillaria* the changes were similar but rather more intense.

When sections of the pre-frontal and pre-central gyri and the pulvinar of the optic thalamus were examined with the oil immersion objective, inclusion bodies were seen also in the cytoplasm of the affected nerve cells. These varied greatly in size. All were eosinophilic, and with Lendrum's phloxin tartrazine method the smaller bodies had a bright red colour, and appeared more sharply defined than with eosin staining. It was also possible to pick out with ease the more granular bodies which were difficult to distinguish from the cytoplasm of degenerated cells in sections stained with eosin. The smallest bodies resembled those illustrated in figs 1 to 4 and usually lay at the periphery of the cell. As these bodies became more numerous they appeared to become collected in a mass most often near the cell margin in one sector of its circumference, but not infrequently they formed a streak along the centre of the apical dendrite (fig. 14). Later the granules appeared to fuse into a hyaline mass which took a more orange stain with Lendrum's method; this might form a horseshoe round the outer half of the cell body with its ends based on the eccentrically displaced nucleus (fig. 15). Finally the nucleus and the cell body appeared to be lying side by side, the latter having been entirely transformed into a hyalinized shrunken mass (fig. 16). The two latter stages appeared under rather lower magnifications as the eosinophilic hyalinization of the cytoplasm already described.

The cells showing these larger cytoplasmic inclusions always also contained intranuclear inclusions, which in general were smaller in cells with small intracytoplasmic inclusions, and filled the nucleus more completely in cells with larger cytoplasmic inclusions. Cells containing the smaller, more granular inclusions might have one or more small intranuclear inclusions, but some appeared to have quite normal nuclei.

In the *corpus luysii, substantia nigra* and *nucleus ruber* there was some fibrous gliosis with slight increase of microglia, but no degeneration of neurons was seen.

In the *pons* there was rather severe perivascular infiltration and microglial proliferation in the nuclei pontis with slight fibrous gliosis. In some of these neurons intranuclear inclusion bodies were seen, and they were often associated with the presence of cytoplasmic granules which stained purple with Mallory's phosphotungstic acid hæmatoxylin. The tegmentum and its nuclei were little affected.

The *cerebellar cortex* showed more obvious changes in this case than in the others. Although the Purkinje cells showed little change and no inclusion bodies were seen in them, many had probably disappeared and there was a fairly diffuse fibrous gliosis of the molecular layer. This was in most places slight in degree, but in some places was rather more definite and was associated with a local excess of microglial cells, which either formed a fairly narrow band passing through the thickness of the molecular layer, or a wider area confined to the inner half or two-thirds of this layer. In the thionin-blue sections the cells sometimes showed their cytoplasm in the fashion described by Spielmeyer as "bush work" (gliastrauchwerke). In most cases, however, only the nuclei were seen. The former appearance which was seen by Spielmeyer in typhus fever probably represents the earlier stages of a local microglial reaction secondary to the degeneration of Purkinje cells.

The Inclusion Bodies

In Case 1 only could any granularity be seen in the intranuclear inclusions. In the other three cases they appeared quite hyaline in magnifications up to × 900. They were round or oval with a well-defined highly refractile margin. When they were smaller than the nucleus of the cell they usually lay centrally, pushing the nucleolus to one side and leaving a clear zone between them and the nuclear membrane on which the remaining chromatin was condensed. Many inclusion bodies filled the nucleus completely and only a few granules of chromatin could be seen on their surface. The smallest single inclusions, e.g. those in the inferior olives of Case 2, were about 3 μ in their narrower diameter; the majority of those in the cortical pyramids varied from 5 to 6 μ and the largest, i.e. those in the ventral horns of Case 2, reached 10 μ in their narrower diameter. The small multiple bodies seen in the ventral horn cells in this case were less than 1 μ in diameter. None of these inclusions was stained by Bielschowsky's silver method. With Ehrlich's hæmatoxylin and eosin they were eosinophilic, but did not stain quite so brightly as red blood cells, and they often appeared rose pink or even mauve in colour, according to the intensity of the eosin stain. With Mallory's phosphotungstic acid hæmatoxylin they stained purple or lavender contrasting with the pink-staining nucleolus and the reddish-purple cytoplasmic granules. These last were considered to be degeneration products, and as quite different from the eosinophilic intra-cytoplasmic inclusions, which were not easily recognizable by this stain.

In sections from Cases 1, 3 and 4 stained by Lendrum's phloxin-tartrazine method the intranuclear inclusions showed a variable affinity for the phloxin; some were quite brightly stained but many showed gradations to orange. The orange examples were usually those that filled the nucleus completely. Sections from Case 1 have also been stained and examined by Lendrum, who reports (1947), "a relatively poor phloxinophilia." The smaller cytoplasmic inclusions on the other hand were uniformly and brilliantly phloxinophil in all three cases.

The cytoplasmic inclusions also stained with eosin rather more brightly than the intranuclear inclusions, i.e. almost as brightly as the red blood corpuscles. The multiple intranuclear inclusions seen in the inferior olives and ventral horn cells of the cervical cord in Case 2 appeared to represent an earlier stage than the larger single bodies, as the cells in which they were found often showed little evidence of degeneration. It appeared probable that the larger bodies were formed by coalescence of small bodies and some evidence of this in the form of lobulated inclusion bodies was seen in a few cells of the cervical cord of Case 2.

Similarly the cytoplasmic inclusions, of which the smaller examples

were usually multiple, appeared to fuse into larger bodies and eventually replaced the whole of the cytoplasm in many cells in the cortex and optic thalamus of Case IV.

Discussion

The clinical picture in the four patients reported in this paper showed certain common features which may possess diagnostic value: in fact it was experience of Case 2 that enabled the diagnosis to be made in Case 3 during life. All four patients were children between the ages of 4 and 11 years and in each case the illness ran a subacute course ending fatally between nine weeks and six months after the onset. In Cases 2 and 3 the first abnormality noticed was psychological—a change in temperament; in all four the disease produced dementia and quadriplegia, and finally a condition of decortication. Persistent or intermittent muscular spasms were present in Nos. 2, 3 and 4. Signs of meningeal irritation were absent and the cerebrospinal fluid showed no increase in the cellular or protein content, but a Lange reaction of paretic type was found in Case 3, the only one in which fluid was thus tested. The onset and course of this disorder, then, was more insidious than is usual in the forms of encephalitis due to neurotropic viruses in general.

Other cases of subacute inclusion encephalitis.—Our four patients appear to have suffered from the type of encephalitis which was first described by Dawson in 1933, and called by him "inclusion encephalitis." His patient was a boy of 16 whose illness started with involuntary jerking movements of the arms and legs, along with loss of self-control. The illness lasted about seven weeks till death. On post-mortem examination the brain was described as congested and œdematous and on microscopical examination, in addition to the usual evidence of encephalitis, eosinophilic inclusion bodies were found in the nuclei of degenerated nerve cells, and also refractile hyaline eosinophilic inclusion bodies in the cytoplasm. Similar intranuclear inclusions were seen in swollen astrocytes. A year later Dawson published a second case in a girl of 5 years in whom also the early stages of the disease were characterized by peculiar jerkings of the limbs. When admitted to hospital three months later, these jerkings had become more frequent and severe, she had lost the ability to speak and was so stuporose that she did not eat. The cerebrospinal fluid in this case was normal. As in the previous case the limbs assumed a lead-pipe rigidity before death, which occurred four months from the date of the first symptoms. The post-mortem findings in this case were similar to those in the previous one. Injections of brain emulsion from both cases were made into rabbits by the intracerebral, subcutaneous and corneal routes without result. Inoculations were also made into mice, rats, monkeys, dogs, cats and chickens without any effect.

In 1942 a similar case was published by Akelaitis and Zeldis. The patient was a boy of 5 years, whose illness started twelve days before admission. One night he had awakened crying and frightened and the next morning there was stiffness and twitching of the left arm. Five days later the left leg began to twitch and became rigid and these movements progressed to severe dystonic movements causing him to fall backwards. On admission to hospital he was semistuporose and dysarthic, but was well orientated and responded slowly to questioning. There were hyperkinetic seizures like rapid torsion spasms on the left side, with arching of the back, but not of the neck, to the left. Between the seizures the left arm and leg were spastic, the leg in extension, the arm in flexion and adduction. The cerebrospinal fluid was normal, except for the presence of a strong paretic curve in the Lange reaction. A week after admission to hospital the jerking spread to the right limbs and there was dystonia of both sides of the body. Dysphagia and dysphonia supervened with transient ocular palsies. He died nine weeks after the onset of the illness. Post-mortem, the brain was swollen and soft with large areas of cortical necrosis on the lateral and inferior surfaces of the right frontal lobe, in which irregular cyst-like spaces were also seen, and there were smaller discrete areas of necrosis in the left occipital cortex. The microscopical examination of the less-affected areas of the cortex gave similar results to those in Dawson's cases, inclusion bodies being seen in many degenerated neurons and also in oligodendroglial cells. There were also cytoplasmic inclusions of doubtful nature in the nerve cells. These did not resemble the intranuclear inclusions. No attempt to isolate the virus was made in this case.

Acute forms of inclusion encephalitis.—Under the title "Intranuclear inclusions in infancy," Kinney published in 1942 the case of a child of 3 years. The illness began with a convulsion, and attacks of trembling and crying. Three days later more convulsions occurred. The child was admitted in a semistuporose condition to hospital, where no abnormal physical signs were found except constant twitching of the lips. Convulsions became more severe, the child became comatose and died about seven days after the onset of illness.

Post-mortem examination showed no gross abnormality, but microscopical lesions of encephalitis were found in all areas of the brain; none was seen in the spinal cord. In the cortex and subcortical white matter there were focal areas infiltrated with polymorphonuclear and mononuclear cells. These were perivascular in the white matter, but more diffuse in the grey, a few areas of which were partially necrotic. In some areas intranuclear inclusions were seen in the nerve cells. The walls of some blood-vessels in this case were necrotic and infiltrated by polymorphonuclear cells and macrophages, and one intranuclear inclusion

was found in a cell of the vessel wall. The inclusion bodies were acidophilic and granular. No inoculation experiments were made in this case. No disease was found at a lower level in the brain than the substantia nigra.

Another acute case in a male aged 21 was published in Australia in 1943 by Swann. The patient was a diabetic, but under control with protamin-zinc-insulin. A fortnight before admission he had had a severe cold with herpes labialis. The illness began with 12 "spasms" during one night in which the patient felt his tongue swollen. He was admitted to hospital next day with left-sided facial paralysis. Glucose and acetone were found in the urine. He had attacks of twitching and two epileptiform attacks when in hospital, and he died nine days after the onset of the illness. Post-mortem examination showed foci of necrosis in the deeper layers of the cortex, often perivascular in distribution and associated with total destruction or partial degeneration of axons and myelin. There was also degeneration of the walls of many vessels, associated with a fibrinous exudate with degenerated polymorphonuclear and microglial cells in the extra-adventitial tissues. The coalescence of necrotic foci led to larger areas of softening under the most severely damaged areas of cortex, similar perivascular areas of degeneration were seen in the white matter. Intranuclear inclusion bodies were found both in nerve cells and in astrocytes and oligodendroglia.

These last two cases have several points in common and differ from the other three in the acuteness of their course and in the evidences of necrotic changes in the walls of the blood-vessels. As no inoculation experiments appear to have been made in either case it is impossible to state whether or not they may have been the results of infection by the virus of herpes febrilis; the occurrence of herpes simplex on the lips in the Australian case a fortnight before the onset of the encephalitis is suggestive in this respect. This suggestion is supported by a case published by Smith, Lennette and Reames in 1941. An infant 4 weeks old was well till four days before admission to hospital when it became irritable and fretful. On the day before admission to hospital there was twitching of the left arm and leg which continued. There were also occasional convulsions. Death occurred on the ninth day of illness. Microscopically the brain showed an extensive inflammatory process in the brain tissue and around the meningeal vessels. Apart from slight swelling of endothelial cells no vascular changes were seen, but areas of frank necrosis were seen in the cerebrum and cerebellum. The intranuclear inclusion bodies varied from four to five times the width of the nucleolus to the whole width of the nucleus and as in Swann's case fine radiating lines were sometimes seen connecting the body with the nuclear membrane.

The larger bodies were often granular. In this case innoculation of brain emulsions into mice, rabbits, rats and guinea-pigs gave a virus indistinguishable from that of herpes febrilis.

A similar case of acute encephalitis due to a virus identical with that of herpes simplex was reported in 1944 by Zarafonetis, Smadel, Adams and Haymaker. The patient was a 25-year-old soldier, who complained of headache three days before he was first examined and during that time became slow and incoherent in speech. On examination he was conscious, but apathetic and febrile, with a temperature of 103°F. and a pulse of 108 per minute. Kernig's sign was positive and there was stiffness of the neck. The spinal fluid contained 175 lymphocytes per c.mm. and 44 mg. of protein, with normal glucose. Three days later the fluid was flocculent with over 300 cells, chiefly lymphocytes. The temperature rose to 105°F., he became delirious but no further neurological signs developed. He died eight days after the onset of the disease. Post-mortem examination showed an area of softening along the inferior margin of the left temporal lobe, 4 cm. in diameter. This area was studded with small hæmorrhages. Elsewhere there was intense vascular congestion with small ecchymoses and petechiæ. A meningeal exudate was seen especially round the vessels. The cerebral cortex, mid-brain and pons showed perivascular cuffing, and there was some proliferation of glial cells round the cuffed vessels. Many scattered cortical neurons were in a condition of ischæmic necrosis, even in places at a distance from the area of necrosis. Intranuclear inclusions were present in profusion in the most affected areas, chiefly in the glial cells but a few also in neurons. They were also seen in cells deep in the brain tissue in the areas of glial proliferation. Brain emulsion preserved in buffered glycerine produced encephalitis in mice, hamsters, guinea-pigs and rabbits, but inoculation into a monkey was without result.

Cases of encephalitis in which Type A inclusion bodies have been found thus separate themselves into the relatively subacute type examined by Dawson (1933 and 1934), Akelaitis and Zeldis (1942) and ourselves, and the more acute cases of Smith, Lennette and Reames (1941), Swann (1943), Kinney (1942) and Zarafonetis, Smadel, Adams and Haymaker (1944). In two cases of the latter group inoculation into animals proved that the encephalitis was caused by the virus of herpes simplex. In the former group attempts to inoculate animals in both Dawson's case and in our Cases 2 and 3 were without result. Dawson appears to have used mice, rats, rabbits, cats, dogs, monkeys and chickens without result. In our Case 2 intracerebral injections were made into mice and rabbits both by the intracerebral and corneal routes and in Case 3 into rabbits, mice, guinea-pigs and hamsters also without result. It is possible that after so

prolonged an illness the virus might have been fixed to the nerve cells in such a way as to render its passage to animals more difficult. However, it remains true that three workers failed to transmit the virus to animals from our Case 3 although the case was recognized before death as probably one of inclusion encephalitis and every care was taken to ensure a passage to animals if this were possible. It is to be noted also that Akelaitis and Zeldis state in their paper that Dr. Marguerite Smith considered that the inclusion bodies in their case were "quite distinct morphologically from those in which she isolated the herpes simplex virus."

The cytoplasmic inclusions seen by Dawson and by ourselves are also unlike anything seen after infection with the virus of herpes febrilis. Although these differ to some degree in staining reactions from the intranuclear inclusions, they resemble the inclusion bodies of other virus diseases, and do not appear to be purely degenerative in character. The evidence, therefore, is in favour of the view that the subacute type of case described by Dawson, Akelaitis and Zeldis and ourselves differs ætiologically from the acute cases in which the virus of herpes febrilis has been incriminated.

It is also to be noted that the cerebral lesions in these seven subacute cases were more confined to the grey matter than those in the acute cases. Even though, as in the case of Akelaitis and Zeldis, there may be extensive necrosis of the cortex, it is noted that this "stopped short of the white matter." In the cases we examined it was evident that the encephalitis had attacked the grey matter primarily and that the changes seen in the white matter were secondary to damage to cortical nerve cells.

In this respect the disease contrasts with that of "subacute necrosing leuco-encephalitis" recently described by van Bogaert, in which both white and grey matter appear to be primarily affected, but with much less severe destruction of nerve cells than in Dawson's type. The occasional presence of inclusion bodies in the oligodendroglial cells suggests, however, that the virus responsible for this type of encephalitis may be less strictly neurotropic than, for example, that of rabies.

It is of course possible that more than one form of virus may be responsible for these seven cases, although the close similarity of their histological appearances makes this unlikely. Until further evidence of their ætiology is forthcoming, it would seem advisable to group them together, and to separate them both from the acute cases in which inclusion bodies are present, and from the subacute cases, both of van Bogaert's type, and the other rare subacute cases in which the encephalitis is confined to the grey matter. The term "inclusion encephalitis" suggested by Dawson is therefore not sufficiently distinctive by itself, and we suggest the name "subacute inclusion encephalitis (Dawson type)."

PLATE XVIII

FIG. 1

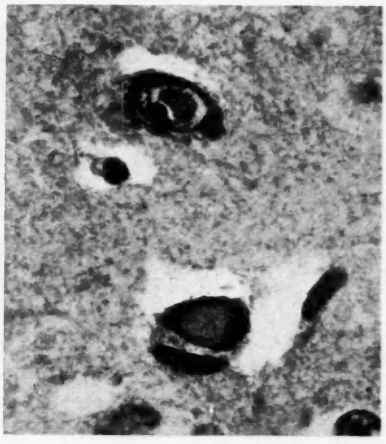


FIG. 2

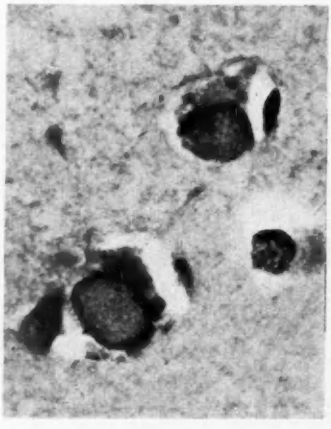


FIG. 3

FIG. 4

To illustrate article by W. Russell Brain, J. G. Greenfield and Dorothy S. Russell.

PLATE XIX

FIG. 5

FIG. 6

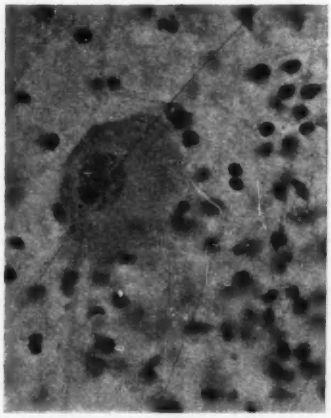


FIG. 7

FIG. 8

To illustrate article by W. Russell Brain, J. G. Greenfield and Dorothy S. Russell.

PLATE XX

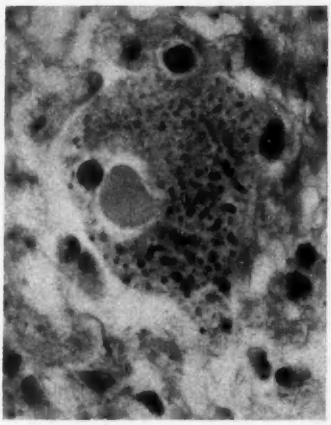


FIG. 9

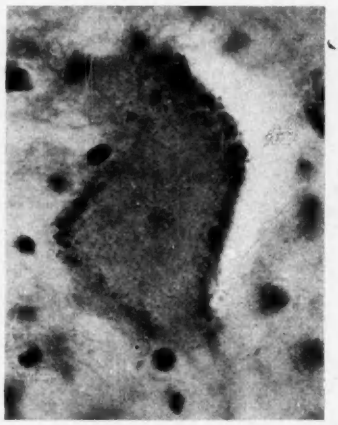


FIG. 10

FIG. 11

FIG. 12

To illustrate article by W. Russell Brain, J. G. Greenfield and Dorothy S. Russell.

PLATE XXI

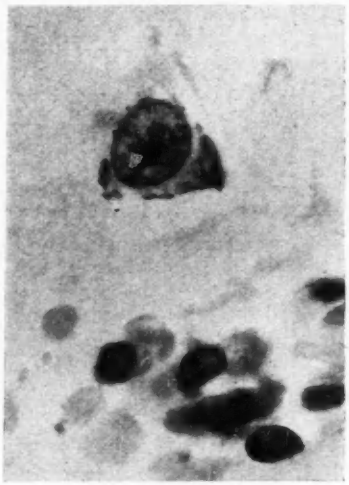


FIG. 13

FIG. 14

FIG. 15

FIG. 16

To illustrate article by W. Russell Brain, J. G. Greenfield and Dorothy S. Russell.

We desire to thank Dr. Macdonald Critchley, whose interest in the case enabled us to obtain material from Case 4, and also Dr. Doyne Bell, under whom the patient was in Charing Cross Hospital, for clinical notes of this case.

SUMMARY

Four cases of subacute encephalitis corresponding to Dawson's "inclusion encephalitis" type are described. The illness ran an ingravescent course, being fatal in from nine weeks to six months, and was characterized by progressive dementia, and in three cases by myoclonic jerking movements of the limbs and face. The cerebrospinal fluid was normal in all four cases except for the presence of a Lange reaction of paretic type in the only case in which it was thus examined.

Post-mortem examination showed subacute lesions of encephalitis which appeared to involve the grey matter primarily, the changes in the white matter being secondary to destruction of cortical nerve cells. Many degenerated nerve cells in the cortex, brain-stem and (in one case) in the spinal cord contained intranuclear inclusion bodies, and inclusion bodies were also seen in the cytoplasm of nerve cells and in the nuclei of oligodendroglial cells. Microglial reaction and perivascular infiltration by lymphocytes and plasma cells were also prominent.

The nature of this form of encephalitis is discussed. It is considered that it differs ætiologically from the acute form of encephalitis associated with Type A intranuclear inclusions, in which the virus of herpes febrilis has been incriminated in all the cases in which animal inoculations have been made. It also differs from the subacute type of encephalitis described by van Bogaert under the name of "subacute sclerosing leuco-encephalitis."

REFERENCES

AKELAITIS, A. J., and ZELDIS, L. V. (1942) Encephalitis with intranuclear inclusion bodies, *Arch. Neur. and Psych.* (*Chicago*), **47**, 353.

BRAIN, W. R., GREENFIELD, J. G., and RUSSELL, D. S. (1943) *Proc. R.S.M.*, **36**, 319.

DAWSON, J. R. (1933) Cellular inclusions in cerebral lesions of lethargic encephalitis, *Amer. J. Path.*, **9**, 7.

—— (1934) Cellular inclusions in cerebral lesions of epidemic encephalitis, *Arch. Neur. and Psych.* (*Chicago*), **31**, 685.

KINNEY, T. D. (1942) Intranuclear inclusions in infancy, *Amer. J. Path.*, **18**, 799.

LENDRUM, A. C. (1947) The phloxin-tartrazine method as a general histological stain and for the demonstration of inclusion bodies, *J. Path. Bact.*, **59**, 399.

SMITH, M. G., LENNETTE, E. H., and REAMES, H. R. (1941) Isolation of virus of herpes simplex and the demonstration of intranuclear inclusions in a case of acute encephalitis, *Amer. J. Path.*, **17**, 55.

SWANN, C. (1943) A case of human encephalitis with Type A intranuclear inclusion bodies, *Med. J. Australia*, **1**, 437.

ZARAFONETIS, C. J. D., SMADEL, J. E., ADAMS, J. W., and HAYMAKER, W. (1944) Fatal herpes simplex encephalitis in man, *Amer. J. Path.*, **20**, 429.

LEGENDS FOR ILLUSTRATIONS

PLATE XVIII

FIG. 1 (*Case* 1).—Cortical neuron containing an inclusion surrounded by the typical halo. The nucleolus (darker) is displaced towards the upper right hand part of the nucleus.

FIG. 2 (*Case* 1).—Two cortical neurons of which the upper contains an inclusion similar to that in fig. 1. The lower cell is at a later stage of degeneration and the inclusion occupies the nucleus more completely. Acidophilic *cytoplasmic* inclusions are also seen near the lower margin of the cell.

FIG. 3 (*Case* 1).—Advanced degeneration in two cortical neurons, in which inclusions fill the greater part of the nucleus. Acidophilic masses are seen in the cytoplasm of the lower cell.

FIG. 4 (*Case* 2).—Two neurons from pyramidal layer of hippocampal cortex, containing intranuclear acidophilic inclusions surrounded by a halo. Acidophilic inclusions are also seen at the margin of the cytoplasm of both cells.

All sections stained with Ehrlich's hæmatoxylin and eosin and magnified × 900.

PLATE XIX

Case 2.—Neurons from the anterior horns of the seventh and eighth cervical segments of the cord; stained by Ehrlich's hæmatoxylin and eosin to show varying numbers and appearances of intranuclear inclusions. All neurons show varying degrees of chromatolysis.

FIG. 5.—Neuron showing three small intranuclear inclusions. Other small inclusions are not clearly in focus. × 800.

FIG. 6.—Neuron showing a larger and a smaller rounded intranuclear inclusion (grey). × 600.

FIG. 7.—Neuron with a lobulated intranuclear inclusion suggesting the fusion of several smaller bodies. × 500.

FIG. 8.—Neuron with a single large hyaline inclusion. × 750.

PLATE XX

FIG. 9.—Anterior horn neuron from eighth cervical segment of Case 2 stained by phosphotungstic acid hæmatoxylin and showing an intranuclear inclusion (grey violet) and numerous degeneration granules in the cytoplasm (reddish purple). To contrast with the acidophilic cytoplasmic inclusions in fig. 10. × 900.

FIG. 10.—Anterior horn neuron from eighth cervical segment of Case 2, stained by Ehrlich's hæmatoxylin and eosin and showing four rounded eosinophil bodies along the right-hand margin of the cell. The nucleus is not present in this section. × 700.

In both figs. 9 and 10 a Wratten B (green) filter was used.

FIG. 11 (*Case* 3).—Cortical neuron stained by Lendrum's phloxin-tartrazine method. × 1750. There is a medium-sized intranuclear inclusion. A fairly large phloxinophilic cytoplasmic inclusion is seen on either side of the nucleus and several small granular inclusions in the cytoplasm near the base of the cell. Yellow filter.

FIG. 12 (*Case* 4).—Pyramidal neurons from motor cortex stained by Ehrlich's hæmatoxylin and eosin and showing intranuclear inclusions and a shrunken hyaline cytoplasm. Note also the microglial hyperplasia. × 800.

PLATE XXI

Case 4.—Neurons stained by Lendrum's phloxin-tartrazine method to show inclusion bodies. Figs. 13, 14 and 15 from frontal cortex. Fig. 16 from pulvinar of optic thalamus.

In fig. 13 the bodies are small, granular or fleck like and lie on the margin of the cytoplasm. A group of plasma cells is included in the photograph. × 1150.

Fig. 14 shows a less common arrangement of granular inclusion bodies round the nuclear membrane and running up the centre of the cytoplasm towards the apical dendrite. × 750.

In both figs. 13 and 14 the cytoplasmic inclusions were stained bright red.

Figs. 15 and 16 show later stages of neuronal degeneration with both cytoplasmic and intranuclear inclusions. × 1100.

In fig. 15 there is a horseshoe-shaped group of hyaline flocculent inclusions in the cytoplasm and a medium-sized intranuclear inclusion.

In fig. 16 the cytoplasm contains a more rounded hyaline mass and the very eccentric nucleus is filled by the inclusion body. In figs. 15 and 16 the inclusions are stained orange.

THROMBOSIS OF INTRACRANIAL VEINS

BY

DAVID KENDALL

Thrombosis of intracranial sinuses and veins was a well-recognized entity among the clinicians of the nineteenth century, and two main varieties were known; simple or primary thrombosis, and secondary or septic thrombosis (Gowers, 1893; Taylor, 1899). The former, occurring at the extremes of life, was commonly associated with prolonged exhausting illness, malnutrition, persistent diarrhœa, leukæmia, tuberculosis and typhoid fever. In this group also were the venous thromboses complicating chlorosis (Bristowe, 1888; Dickenson, 1896; Taylor, 1899; Sallés, 1913). The secondary variety was associated with septic conditions of the skull, scalp and face or with a generalized septicæmic illness. This type of thrombosis is comparatively common at the present time, and is of considerable clinical importance in view of the similarity of the symptoms and signs thereby produced to those of intracranial abscess.

The primary thromboses are now a relative rarity, but interest in them has been revived by the observations of Symonds (1937, 1940), Martin and Sheehan (1941), Martin (1941, 1944), Stansfield (1942), that intracranial venous thrombosis may complicate the puerperium.

In this paper two groups of patients are described; the first group includes 5 patients in whom cerebral venous thrombosis was diagnosed following childbirth, the second includes 6 patients in whom the condition was associated with local or generalized sepsis. Two patients in the latter group were also pregnant.

Cerebral Venous Thrombosis in the Puerperium

Over a century ago, Ménière (1828) published his paper in which he gave an account of a series of patients who suffered cerebral vascular catastrophies after childbirth, the majority of his patients developed some degree of paralysis, and in some the latter was preceded by convulsions. Churchill (1854) gave an account of paralysis occurring during gestation and childbirth. Of his 12 puerperal cases all developed some degree of unilateral paralysis from one to twenty-eight days after delivery, 2 patients had convulsions preceding the paralysis, and in the majority severe head-

ache was an outstanding premonitory symptom. Three of these patients died, but only one autopsy was performed, this revealed the presence of air in the sagittal sinus. Poupon (1885) in an account of puerperal aphasia, which, in his 12 patients, occurred two to twenty-seven days after delivery, recorded that fits preceded the paralysis in 5 cases. Collier (1891) described a case confirmed at post mortem. Gowers (1893) recognized the occurrence of cerebral venous thrombosis in the puerperium, and Sinclair (1902) suggested that puerperal aphasia had a thrombotic basis, basing his suggestion upon the fact that his patient had a venous thrombosis in the leg at the time of the cerebral catastrophe. Hösslin (1904) reviewed the published cases, and Myrick in 1910 described a patient in whom very severe headache developed ten days after a normal delivery, followed in twenty-four hours by repeated focal convulsions and death in three days. Autopsy showed the presence of firm grey clot in the sagittal sinus and in the cortical veins. A very detailed account of a case that came to autopsy was given by Ramsey Hunt (1917). In this case, headache, vomiting and fits followed twenty days after a normal confinement. Death took place after ten days of gradually increasing hemiparesis and stupor. Post mortem, extensive softening of the fronto-parietal cortex was found on one side, with thrombosis of the sagittal, lateral and petrosal sinuses and of the superficial cerebral veins. Careful examination of the pelvis showed no evidence of infection or of thrombosis of pelvic veins. The subject is also discussed at some length by Alpers and Palmer (1929).

Reference has already been made to the series of intracranial venous thromboses reported by earlier writers to occur in chlorosis. That this now extinct iron deficiency anæmia may not have had a uniform ætiology is suggested by certain of the reported cases. Bristowe (1888) reported a case which came to autopsy, where extensive thromboses of the sagittal and lateral sinuses and of the veins of one hemisphere were found, together with evidence of a six-weeks' pregnancy. Dickenson (1896) reported a similar case with the finding of a persistent corpus luteum at autopsy. The findings in these 2 cases suggest that "chlorosis" complicated by sinus thrombosis was in fact none other than the condition under consideration here.

The patients described below conform closely in their clinical features to those described by Symonds, Martin and Sheehan, Martin, and Stansfield. In none of this series was the condition fatal, but in all there seemed little doubt of the diagnosis on clinical grounds alone.

Case 1.—A married woman aged 32 was delivered of a healthy child at term on 20.7.47. Pregnancy and labour were normal. On 10.8.47, after the patient had been ambulant for one week, she complained of intense frontal headache and almost

immediately had a generalized convulsion, after which she remained stuporose for three hours. On recovering consciousness she complained of tingling in both feet which also felt weak. On examination, the patient was drowsy but co-operative, the cranial nerves were normal, there was very slight nuchal rigidity, the upper limbs were normal; in the lower limbs some weakness of dorsiflexion of both feet was present, and both plantar responses were extensor. Later the same day three further fits took place, on each occasion they commenced by twitching in the lower limbs, followed within a few seconds by generalized convulsions. The cerebrospinal fluid was under a pressure of 300 mm./water, was faintly cloudy, and contained 500 R.B.C./c.mm. Total protein was 65 mg. per cent. A diagnosis of sagittal sinus thrombosis was made and treatment with heparin 150 mg. b.d. and dicoumarol 100 mg. b.d. was commenced. The blood at the commencement of this treatment contained 450,000 platelets per c.mm. and the prothrombin time was twelve seconds. Phenobarbitone was administered as a precaution against further fits. The following day the patient was alert, and complaining of severe frontal headache; examination of the ocular fundi showed engorgement of the retinal veins with hyperæmia of both optic discs. On the third day, in spite of subjective improvement, frank papillœdema was found (2 D right and left). On the fifth day the physical signs were unchanged, but the prothrombin time had risen to forty-eight seconds, anticoagulant treatment was therefore discontinued. On the tenth day a small uterine hæmorrhage occurred which ceased spontaneously, papillœdema persisted and both plantar responses remained extensor. The cerebrospinal fluid pressure had fallen to 250 mm./water, and the fluid was faintly yellow, containing 90 mg. per cent of protein. From this time steady improvement took place, and by the fifteenth day, lumbar puncture, which had been performed daily, was discontinued, the pressure having fallen to 130 mm./water. The patient returned home on the twenty-seventh day, free from abnormal symptoms and signs. She has remained well since that time and has taken regular small doses of phenobarbitone as a precaution against further fits.

Comment.—The onset with convulsions followed by weakness in the lower limbs and signs of raised intracranial pressure together with the presence of red blood corpuscles in the cerebrospinal fluid constitutes the characteristic clinical picture of occlusion of the sagittal sinus. It is difficult to assess the value of anticoagulant treatment, but the fairly rapid recovery suggests that a relatively small thrombosis was prevented from spreading. The uterine hæmorrhage is a warning against the overuse of this therapy.

Case 2.—A married woman aged 27 was delivered of twins one month prematurely on 28.12.47. Pregnancy had been normal apart from some œdema of the ankles. Labour required the minimum of interference and lasted four hours. There was no abnormal bleeding. A few hours after delivery the patient complained of severe frontal headache with nausea, and nine hours after delivery a generalized convulsion occurred. For the next twenty-four hours her condition improved. Forty-eight hours after delivery very severe frontal headache returned and it was then found that she was having difficulty in expressing herself verbally. During the next twenty-four hours the speech difficulty increased and some weakness in the right arm and leg was noticed. On the fifth day after delivery complete motor aphasia was present, with very slight weakness in the right upper limb, the right plantar response was extensor. Temperature remained normal throughout, but the pulse was rather slow, *circa* 60. No abnormality was detected in the pelvis.

A diagnosis of venous thrombosis in the left frontal region was made and treatment with heparin 150 mg. and dicoumarol 100 mg. twice daily was commenced

and continued for three days. At the end of this time the prothrombin time was forty-six seconds. Power of speech returned very rapidly and was normal within ten days from the onset. The right-sided weakness disappeared simultaneously. On the fourteenth day after delivery (ten days from the commencement of anti-coagulant therapy) a severe uterine hæmorrhage occurred (about two pints). This was controlled with ergometrine, and a transfusion of two pints of blood was given.

The patient returned home on the twenty-fourth day, free from symptoms.

Comment.—The relatively slow evolution of symptoms in this case seems very characteristic of non-pyogenic venous thrombosis. No lumbar puncture was performed, but there was no clinical evidence of raised intracranial pressure. This suggests that cortical veins were involved and that there was probably no obstruction to the absorption of cerebrospinal fluid by a thrombus in the sagittal sinus.

Case 3.—A married woman aged 33 was delivered of her third child on 11.9.45. Labour was normal. On the third day post partum there was some pain in the left thigh, the temperature was raised to 100° F. and the leg became moderately œdematous. On the sixth day the patient complained of headache, and repeated twitching of the right hand was noticed. Later the same day, a succession of right-sided epileptic attacks occurred, commencing in the hand. Power of motor speech was lost, but consciousness remained. The attacks were controlled with phenobarbitone. Lumbar puncture on the seventh day showed a normal fluid under normal pressure. A mild right hemiparesis persisted for approximately one week, during which time motor speech was gradually restored. At the end of fourteen days no neurological abnormality was detected.

This patient first came under the care of the writer on 20.8.46. She was admitted to hospital having been found unconscious in her home. She was conscious on admission, but had a complete motor aphasia. The right side of the face was weak, and the right arm was hypotonic and weak. About one hour after admission an epileptic attack occurred, commencing in the right arm and rapidly becoming generalized with loss of consciousness. On recovery the right-sided weakness was more marked. All investigations, including air-encephalography, were negative, and the physical signs present rapidly disappeared. When last seen in December 1947 the patient had remained well and no further attacks had occurred. There was no previous or family history of epilepsy in this case.

Comment.—The inference to be drawn from this case is that some degree of permanent damage may result from thrombosis of a cerebral vein and this damage may subsequently result in epileptic attacks. It suggests that this diagnosis is an indication for prolonged medication with phenobarbitone.

Case 4.—A married woman aged 26 had her first confinement at home on 7.9.47. She was admitted to hospital the following day having had a severe post-partum hæmorrhage. Blood-count showed R.B.C. 1·7 million; hæmoglobin 32 per cent; W.B.C. 12,600. Blood transfusion was carried out, and apart from a pyrexia up to 100° F. for four days her condition improved until 18.9.47. On this day she felt faint after straining on the bedpan, shortly afterwards twitching of the mouth was noticed followed by a generalized convulsion. On recovery she complained of left parietal headache and numbness of the right arm. Examination the following day revealed no abnormal physical signs. On September 20, 21 and 22 several further generalized fits took place, following which there was a severe motor and receptive dysphasia with weakness and inco-ordination of the right arm. Lumbar puncture showed the cerebrospinal fluid to be under normal pressure, the fluid was normal

in all respects. No further fits occurred and by 1.10.47 neurological examination was negative.

Comment.—Two important features arise from the account of this case; the preceding hæmorrhage and the onset of cerebral symptoms while straining on the bedpan. These are discussed further below in considering the ætiology of venous thrombosis.

Case 5.—A married woman aged 25 was admitted to hospital on 24.11.47. Her second baby had been born four months previously, labour and the puerperium were uneventful apart from some swelling of both feet during convalescence. Two weeks before admission there was a gradual onset of pain in the back of the neck radiating to both shoulders. One week later diplopia commenced suddenly.

On examination, the patient was well built, rather pale and in pain. There was bilateral papillœdema of about 3 D, a right external rectus weakness, a rather doubtful nystagmus on fixing to the left and a left extensor plantar response. Temperature and pulse were normal, blood-count was normal, and there was no radiological evidence of an intracranial lesion. Wassermann reaction was negative.

A diagnosis of intracranial tumour was made, with probable localization in the posterior fossa of the skull, and the patient was transferred to the National Hospital, Queen Square, under the care of Mr. Harvey Jackson. Lumbar puncture was performed and the pressure found to be 200 mm./water. The cerebrospinal fluid was normal. Ventriculography showed the ventricular system to be normal and a diagnosis of sagittal sinus thrombosis was made. An uninterrupted recovery took place and when seen on 19.1.48 there were no symptoms, and the papillœdema was subsiding. On 1.3.48 the ocular fundi were normal.

Comment.—This patient presented symptoms and signs indistinguishable from those of intracranial tumour. The diagnosis rested upon the finding of normal ventricles and was confirmed by the favourable progress made. The long interval (four months) between confinement and the onset of cerebral symptoms is unusual, but reference to such an interval is to be found in the literature. Stander (1945) mentions the condition occurring several weeks after delivery, and Stansfield (1944) in a survey of recorded cases states that the condition may arise from the 4th to the 137th day post partum.

Symptomatology and Diagnosis

The main clinical features of the cases reported above correspond closely to those of previously reported cases. Headache is a very constant early symptom and may be generalized or unilateral, in which latter case the pain is localized to the presumed side of the lesion. Convulsive phenomena are common and were present in the first four of the patients reported here. The fits may be focal or generalized, or the attack may commence on one side and spread to involve all the limbs. The fits are usually associated with, or followed by symptoms and signs indicative of a localized cerebral lesion, and it is important to note that such symptoms and signs are relatively slow in their development, and may not be fully established for several hours or even days. Frequently it appears that there

is an increase of weakness in a limb after it has been the subject of a focal epileptic attack. Evidence of raised intracranial pressure may or may not be present and is clearly closely related to the extent and site of the thrombus. The presence of papillœdema must be taken to indicate interference with absorption of cerebrospinal fluid either by mural thrombi in the sagittal sinus or by complete occlusion of that structure. Other symptoms and signs depend entirely upon the site of the lesion and include all degrees of mono- or hemi-paresis, with or without disturbance of sensation. Bilateral weakness of the legs may be present if the sagittal sinus is occluded. Disturbance of speech is likely to occur if the limbs on the right are involved. In one of the patients reported by Martin (1941) complete amaurosis was present. Evidence of venous thrombosis in the pelvic or leg veins may be present.

The cerebrospinal fluid is likely to be normal unless the thrombosis is extensive, in which event a small number of red blood cells may be present. Differential diagnosis does not as a rule present great difficulty once the condition is fully developed. Fits occurring in the puerperium may result from idiopathic epilepsy, or from a pre-existing eclamptic state. The onset of eclampsia after delivery of the child is rare, and is accompanied by the characteristic changes in the urine, with raised blood-pressure and possibly changes in the ocular fundi. Arterial embolism is unlikely in the absence of a cardiac lesion, and when it occurs is likely to produce its maximum effect in a few minutes, unlike cerebral venous thrombosis in which the evolution is relatively slow. Cerebral abscess is unlikely in the absence of an obvious source of infection, and cerebral tumour is no more a hazard of the puerperium than of any other period of life.

It seems clear, therefore, that the occurrence of convulsions, headache and varying degrees of paresis in the puerperium is likely to be the result of thrombosis of a sinus or vein within the cranial cavity, and that the association of papillœdema with this triad places the diagnosis beyond doubt. Further confirmation is forthcoming from the tendency to spontaneous recovery in a relatively short time, and the remarkable completeness of such recovery.

Ætiology

The circumstances that lead to intracranial venous thrombosis in the puerperium have not been determined with any certainty. Two possibilities exist; either that the thrombosis is primary, arising from some local cause in the vein or sinus, perhaps associated with alteration in the circulating blood, or that it arises secondary to thrombosis elsewhere and is initiated by an embolic process. Consideration must be given to factors, if any, in favour of the former hypothesis. It is known that in the

puerperium certain changes are present in the blood. Thus at this time it is found that the number of blood platelets is increased by about 30 per cent (Dawbarn, Earlham and Howell Evans, 1928), and an even higher figure may be recorded if hæmorrhage has been severe after delivery (Bland and Goldstein, 1932). The plasma fibrinogen content is raised in the puerperium, and Gilligan and Ernstein (1934) have observed that the raising of the plasma fibrinogen is proportional to the erythrocyte sedimentation rate. Wright (1942) has made the interesting observation that after hæmorrhage (and therefore presumably after labour) there is an increased "stickiness" of the circulating blood, due, he suggests, to the presence therein of large numbers of newly-formed cells recently discharged from the bone-marrow. The same writer found that the coagulation time is shortened after hæmorrhage. There are, therefore, three factors present in the blood of puerperal patients conducive to the occurrence of thrombosis; an increase in blood platelets, an increase in plasma fibrinogen and an increased "stickiness" of the blood. Nevertheless, these factors alone will not initiate a thrombus; there must first of all be some damage to the endothelial lining of the vessel concerned with or without the added element of stasis of the blood flow therein. It is clear that both the last-mentioned factors may be operative after labour; during that act, in consequence of the greatly increased intra-abdominal tension and the forced expiratory efforts against a closed glottis, there is necessarily a very considerable intermittent rise in the intracranial venous pressure. The element of stasis is present, and the high pressure may well be sufficient to damage the somewhat fragile walls of the intracranial sinuses or veins. Thus a small mural thrombus may be formed and the process visualized by Aschoff (1924) initiated. A white mural thrombus, consisting of platelets and leucocytes only, is gradually built up until it reaches a size sufficient to obstruct or very materially slow the blood flow in the vessel. A normal red clot is then formed, consisting of the blood elements in their normal proportions and the occlusion of the vessel is completed. In this way it would be possible to account for the delay in the onset of symptoms after labour, and the relatively slow evolution thereof.

Batson (1940), in the course of an investigation into the route taken by metastatic fragments of tumours, found that radiopaque substances injected into the dorsal vein of the penis in the cadaver found their way into the vertebral venous system. He repeated the experiment using live Rhesus monkeys, and obtained the same result, provided the intra-abdominal pressure was raised by the application of a tight binder. Martin (1941) suggested that puerperal venous thromboses might arise in a like manner. He suggested that a primary thrombus occurred in the pelvic veins, and that the raised intra-abdominal pressure associated with

parturition caused a fragment to be detached, and to pass into the vertebral venous system, thence to an intracranial vessel. As a point in favour of this hypothesis, Martin drew attention to the fact that one of his patients in whom the diagnosis of intracranial venous thrombosis was made subsequently died of a spinal lesion. In this connexion it is of interest to note the numerous cases of puerperal myelitis reported in the literature by Brush (1898), Hamill (1895), Marinesco (1924), Alpers and Palmer (1929), and to note that the descriptions of some of these cases is very suggestive of a vascular rather than an inflammatory basis for the condition.

There are various points both in favour of and against this hypothesis Foremost in its favour is the work of Batson, together with the known absence of valves in the greater part of the vertebral venous system. The rise in intraspinal pressure consequent upon a rise in intra-abdominal pressure is a well-known phenomenon in the course of routine lumbar puncture. Finally, the known presence in the circulation of chorionic fragments after parturition renders even the postulation of a primary pelvic thrombus unnecessary.

Against this hypothesis is first the fact that Batson, in the course of his experiments, was only able to produce filling of the intracranial sinuses in the cadaver and that only after injection into a vein of the shoulder girdle. In the living animal the radiopaque material entered the vertebral veins but did not reach the cranium. During labour, there is no doubt that the intra-abdominal pressure is raised, probably to a sufficient extent to redirect the return flow of blood from the inferior vena cava to the vertebral system, but so also is the intrathoracic pressure raised, and thence the pressure in the internal jugular veins and in the intracranial sinuses. This latter rise in pressure may well be sufficient to counterbalance if not to overcome the raised pressure from below, since it has to assist it the normal direction of blood flow.

The vertebral venous system, although devoid of valves, is tortuous and plexiform, and communicates with the intracranial venous system via the condyloid emissary veins which run into the lateral sinuses, and the inferior petrosal sinuses, the latter being the main connexions (Gray's Anatomy, 1930). Thus an embolus arising in the pelvis would of necessity be small and would have to traverse a very irregular and tortuous path to reach, for instance, the sagittal sinus. Having arrived at its destination, it would be necessary to postulate that the embolus causes some endothelial damage and thereby forms the nucleus of a thrombus. In no other way would it be possible to account for the delayed onset of symptoms. In this connexion it should be pointed out that it has been shown that the experimental production of sagittal sinus thrombosis by

mechanical means is exceedingly difficult if not impossible. Beck (1944) tried the effect of mechanical occlusion, chemical coagulants and the two methods combined, using rabbits, cats and dogs for the attempts; all were unsuccessful.

Martin (1941) found evidence of a primary thrombosis in the pelvic region in 3 patients, and Martin and Sheehan (1941) found such evidence in 2 of 5 patients. Symptoms suggestive of thrombosis of leg veins were present in 2 of the present series of patients. In the case so fully described by Ramsey Hunt, no pelvic abnormality was found at autopsy. The inconstancy of thromboses in the pelvic or leg veins in these patients is remarkable in view of the relatively high incidence of this complication after childbirth. Some clinical evidence of this condition is present following two to three of every hundred confinements. One would expect then, if the embolic theory is correct, that evidence of pelvic thrombosis would be present in every case of the far rarer condition of cerebral venous thrombosis, but this is not the case.

Pulmonary embolus following pelvic surgery is a fairly common hazard. Characteristically it occurs while straining at stool some ten days after operation. During this act, the intra-abdominal pressure is raised, but occlusion of cerebral veins is not a recognized complication.

It may therefore be said that a retrograde venous embolus is anatomically possible, but that its occurrence is unlikely for the reason stated above, and it is probable that cerebral venous thrombosis in the puerperium is of a "primary" nature.

Treatment

Prophylactic treatment is not possible in view of the uncertainty of the processes involved, but steps should obviously be taken to avoid the known precursors of venous thrombosis in general; sepsis and undue immobilization.

Once the diagnosis is established the question of the use of anticoagulants arises. These drugs may be expected to discourage the spread of an existing thrombus, but of course will not have any direct effect upon the re-establishment of the circulation. Their use during the puerperium introduces the danger of precipitating uterine hæmorrhage, which might well make the patient's plight worse than before. This complication occurred in both the patients so treated in the present series. If, therefore, treatment of this kind is instituted, the most careful control should be exercised, and the drugs administered for a shorter time than is customary when they are used in other conditions. It is suggested here that the prothrombin time should be estimated twice in every twenty-four hours, and that combined therapy with heparin and dicoumarin should be continued for not more than two days.

Active measures may be required to control repeated epileptic attacks; these may usually be controlled by adminstration of adequate doses of barbiturate drugs. It is suggested that the occurrence of fits is an indication for prolonged sedative therapy for at least a year, with the object of controlling any subsequent epileptic tendency.

When the signs present point to a thrombosis of the sagittal sinus and evidence of raised intracranial tension is present, it is advisable that daily lumbar punctures should be performed, with the object of reducing the pressure. This manœuvre should be continued until the initial pressure of the cerebrospinal fluid has fallen to about 180 mm./water.

Measures to deal with paralysed limbs are not usually required, since spontaneous recovery tends to be rapid, but physiotherapy, when available, no doubt accelerates recovery.

It is not possible at this juncture to make any definite recommendation with regard to future pregnancies, but it would be reasonable to advise against further pregnancy for a period of two years.

Prognosis

The number of reported cases is as yet too small to form any definite conclusion as to the mortality of this condition. About 30 per cent of recorded cases were fatal, but as the condition becomes more frequently recognized the ultimate mortality is likely to be much lower.

Recovery, when it takes place, is usually complete. Only one patient of the present series had a persistent disability; the occurrence of epileptic attacks.

Intracranial Venous Thrombosis Resulting from Infection

Unlike the condition just described, cerebral thrombophlebitis resulting from local or from remote infective conditions is of relatively common occurrence. Earlier writers recognized the condition, but regarded it mainly as a terminal event following upon disease of the ear, nasal sinuses or wounds and infections of the scalp and face. Partly as a result of the recognition of lesser degrees of the condition and partly as a result of modern chemotherapy a more benign form of the condition is now commonly observed.

Interest in the subject has been largely stimulated by the observations of Symonds (1937, 1940, 1944), who was the first to recognize that raised intracranial pressure associated with middle-ear disease may be due to thrombosis of intracranial venous sinuses.

The principal interest of the condition lies in the fact that thrombophlebitis is associated with the same conditions that may give rise to cerebral abscess, and that the differentiation of the two conditions may present considerable difficulty.

The patients described here give some idea of the variable clinical picture.

Case 6.—The patient, a girl aged 13, was admitted to hospital on 29.1.48. Two weeks previously she had had a severe sore throat associated with right frontal headache and pain in the right eye. The throat condition improved, but the headache persisted. Three days before admission a generalized convulsion occurred after which the left arm became weak. At the same time there was complaint of pain in the back of the neck. Examination showed a flushed, restless child, cooperative but drowsy. T. 103°, P. 116. There was marked tenderness over the right frontal sinus and complete obstruction of the right nostril. There was slight neck rigidity. Both optic discs were red, and indistinct in outline, there was a rather doubtful left homonymous field defect, a left facial weakness and weakness of the left half of the tongue. The left upper limb was completely paralysed, the lower limb was weak. The deep reflexes were absent on the left and the plantar response extensor. The cerebrospinal fluid was under pressure of 300 mm./water and contained 34 cells, all polymorphonuclear. Total protein was 50. The fluid was sterile. The diagnosis rested between an extensive right-sided thrombophlebitis and a cerebral abscess. In view of the latter possibility, the patient was transferred to the National Hospital, Queen Square, under the care of Mr. Harvey Jackson. Treatment with penicillin 100,000 units three-hourly and sulphadiazine 1 gramme four-hourly was commenced. On 2.2.48 the cerebrospinal fluid contained 476 cells, 90 per cent polymorphonuclear. On 3.2.48 repeated left-sided fits occurred and were controlled by the intramuscular injection of phenobarbitone. The physical signs present were unchanged. On 4.2.48 the cerebrospinal fluid pressure had fallen to 140 mm./water, and the fluid contained 88 cells. There was a leucocytosis in the blood of 15,000/c.mm. From this day recovery took place rapidly, and was almost complete apart from a little mental dulling by 25.2.48. When seen again on 16.3.48 nothing abnormal could be detected.

Comment.—A diagnosis of cerebral thrombophlebitis was made and was based upon the very rapid onset of cerebral symptoms, the presence of raised intracranial pressure, and the rapid response to treatment. Had the patient survived untreated, cerebral abscess might well have followed, but in the absence of chemotherapy the outcome would have been almost certainly fatal before an abscess had had time to develop.

Case 7.—A man aged 28 was admitted to hospital on 15.5.47. For two weeks prior to admission he had had a cold accompanied by increasingly severe frontal headache, for two days stiffness of the neck had been present, together with repeated vomiting. On admission temperature was 102°, pulse 100. There was moderate neck rigidity. The cerebrospinal fluid was under a pressure of 280 mm./water and contained 150 cells of which 20 per cent were polymorphonuclear, 80 per cent lymphocytes. Penicillin 50,000 units and sulphadiazine 1 gramme four-hourly were commenced. Examination of the blood showed 31,500 W.B.C., 80 per cent polymorphonuclear. On 18.5.47 a generalized convulsion occurred, followed by moderate weakness of the right arm and leg. The following day the cerebrospinal fluid pressure was 280 mm./water, and the fluid contained 380 cells, 90 per cent. lymphocytes. He continued to have frequent generalized convulsions for the next nine days. He was first seen by the writer on 28.5.47, when he appeared drowsy and irrational. There was marked tenderness over the left frontal sinus, and moderate neck rigidity. Bilateral papilloedema was present, the right arm and both legs were weak, both plantar responses were extensor. He was transferred the same day to Horton Emergency Hospital with a diagnosis of extradural abscess, with the possible addition of sagittal sinus thrombosis. The following day a rigor occurred.

The cerebrospinal fluid pressure was 300 mm./water, the fluid contained 10 cells all lymphocytes. On 30.5.47 a left external frontal sinus drainage was performed by Mr. W. I. Daggett. Much foul pus was found in the sinus, the posterior wall of which was opened. No extra- or sub-dural pus was found.

The following day the patient's condition improved, but a rigor occurred. Further rigors occurred on the second, fourth and fifth days. Blood culture was sterile. Penicillin and sulphadiazine therapy was continued, and at the end of five days the temperature was normal and remained so. At the end of a week, the papillœdema was subsiding, the upper limbs were normal, and the lower limbs normal apart from a right-sided extensor plantar response. The patient, though mentally clear, was doubly incontinent, and remained so for a further ten days. By 4.7.47 he was symptom-free. Neurological examination showed no abnormality and he was discharged from hospital. It was felt that there could be no doubt that the cerebral symptoms resulted from thrombosis of the sagittal sinus.

Four weeks after discharge, a generalized convulsion took place, but apart from this, the patient remained well until the beginning of December 1947. He then started to become confused, ill-tempered, untidy and forgetful. After about two weeks he became drowsy and incontinent. He was readmitted to hospital on 31.12.47. At that time there were no localizing signs present in the nervous system. Cerebrospinal fluid pressure was 110 mm./water, and the fluid was normal. White blood count 11,000/c.mm., 76 per cent polymorphonuclear. On 8.1.48, a mild left hemiparesis was present with a left-handed grasp reflex. There was early papillœdema. A diagnosis of right frontal cerebral abscess was made, and he was transferred to the National Hospital, Queen Square, under the care of Mr. Harvey Jackson. On 9.1.48 a right frontal burr hole was made and an abscess cavity aspirated followed by instillation of thorotrast and penicillin. Rapid improvement followed, and after repeated tapping of the abscess operation was undertaken on 12.3.48. The right frontal pole was amputated and a bilocular encapsulated abscess enucleated. On discharge from hospital on 8.4.48 he was physically and mentally normal.

Comment.—The chief interest in this patient lies in the fact that a left frontal sinusitis caused in the first place a sagittal sinus thrombosis, followed after a quiescent interval of six months by a right frontal abscess. The difference in the evolution of the two conditions is very striking. The former was of acute onset, with very grave constitutional disturbance, rigors, and evidence of widespread damage to the nervous system; the latter commenced insidiously, with little constitutional change, minimal neurological signs, normal cerebrospinal fluid, but with marked mental disturbance. It is also of interest that the abscess developed upon the side opposite to the infected sinus. Possibly it arose at the site of an infected and thrombosed tributary of the sagittal sinus.

Case 8.—A boy aged 18 was admitted to hospital on 4.9.47 with a recurrence of right-sided mastoid infection. On 5.9.47 the right mastoid was explored and a large amount of subperiosteal pus evacuated. The cavity was filled with debris which was adherent to the lateral sinus, and the latter structure was inadvertently opened. The sinus was packed with ribbon gauze and the patient returned to the ward in good condition. Local and systemic penicillin therapy was instituted. On 6.9.47 repeated vomiting occurred, with severe right frontal headache. Pulse was 60, temperature normal. Cerebrospinal fluid pressure was 300+ mm./water. The fluid was normal. A diagnosis of otitic hydrocephalus was made, and daily lumbar puncture performed with the object of reducing the intracranial pressure to about

180 mm. on each occasion. Headache was relieved thereby until 14.9.47 when the patient complained of very severe pain in the right eye and double vision. Examination showed the presence of papillœdema, right 2 D, left 1 D, and a right external rectus palsy. The cerebrospinal fluid remained normal apart from a pressure of 300+ mm. It was then found following withdrawal of cerebrospinal fluid to lower the pressure to a readable figure on the manometer, that neither right nor left jugular compression caused the fluid pressure to rise. Similar treatment was continued until 25.9.47 (the packing had been removed from the sinus on 15.9.47) when the fluid pressure was found to be only 150 mm. and the papillœdema appeared to be subsiding. All treatment was discontinued, and at the time of discharge on 31.10.47 the ocular fundi were normal, and the sixth nerve palsy was almost recovered.

Comment.—This patient demonstrates clearly Symonds' (1937) contention that raised intracranial pressure associated with ear disease is due to venous thrombosis. In this patient the result of Queckenstedt's test showed that the left lateral sinus drained only into the right jugular vein, and that, in consequence of the obstruction of the right lateral sinus, the return of venous blood from the cerebral venous system was largely prevented, with consequent hydrocephalus. The occurrence of Gradenigo's syndrome (pain in the distribution of the first division of the fifth nerve, with sixth nerve palsy) bears out Symonds' (1944) suggestion that this syndrome results from occlusion of the inferior petrosal sinus.

The question of cerebral abscess did not arise in this case. The very rapid onset of hydrocephalus without focal signs in the first instance pointed clearly to a vascular basis for the condition. Evidently the mechanical damage to the sinus (with the possible assistance of low-grade infection) caused a slowly spreading thrombosis to spread along the lateral sinus to the superior and thence to the inferior petrosal sinus.

Case 9.—A boy aged 5 years had an attack of measles in June 1947. He remained in poor health after this, eating poorly and losing weight. He complained intermittently of pain in the right ear, but there was never any aural discharge. On 27.11.47 he became febrile and listless and for the following ten days his temperature rose intermittently to 102° F. He was admitted to hospital on 7.12.47, having repeated generalized convulsions. Examination after the fits had ceased showed a thin pale child, poorly co-operative, with a moderate amount of neck rigidity. There was a mild left hemiparesis present. The ear-drums appeared normal, and there was no mastoid tenderness. Cerebrospinal fluid pressure was 230 mm./water, the fluid contained 2,437 cells, 80 per cent polymorphonuclear, total protein 330 mg. per cent, chlorides 530 mg. per cent. Culture of the fluid showed a moderate growth of streptococci and pneumococci. There was a polymorphonuclear leucocytosis in the blood of 52,000/c.mm. The diagnosis was considered to be that of meningitis secondary to otitis media, in spite of the normal ear-drums, with the added possibility of an otogenic abscess in the right temporal lobe. Treatment with penicillin 60,000 units four-hourly was commenced and there was slight clinical improvement. On 10.12.47 neck rigidity was no longer present. Temperature was 102° F. Pulse 150. The cerebrospinal fluid contained 545 cells, 80 per cent polymorphonuclear. Total protein 85 mg. per cent, chlorides 602. Five days later the cell count was only 11/c.mm., 80 per cent lymphocytes. In spite of the marked improvement in the meningeal infection, the left hemiparesis

appeared to be increasing, and in view of its continued presence he was transferred to the National Hospital, Queen Square, under the care of Mr. Harvey Jackson, on 2.1.48. One week later an acute attack of otitis media occurred on the left side, with perforation of the drum. From this time onward recovery took place rapidly, chemotherapy being continued for a further week. On discharge on 1.3.48, the boy was well and displayed only very slight reflex changes as evidence of the past hemiparesis.

Comment.—The final diagnosis in this case was thrombosis of superficial veins over the right cerebral hemisphere, secondary to meningitis, which in turn followed a chronic left-sided otitis media. The long illness, with the insidious onset of cerebral symptoms, was very suggestive of abscess formation, but there was nothing to indicate the source of infection other than the history of earache. The ultimate incrimination of the left ear was a surprising development, and the rapid recovery following drainage of this gave support to the diagnosis of venous thrombosis.

Case 10.—A woman aged 33 was admitted to hospital in labour, and with a fever of 104° F. on 24.2.48. Delivery took place shortly after admission. A diagnosis of right-sided pneumonia was made and treatment with penicillin 100,000 units three-hourly and sulphadiazine 1 gramme four-hourly was started. Moderate pyrexia continued, and on 2.3.48 blood culture produced a profuse growth of a penicillin-sensitive strain of *Staphylococcus aureus*. The blood contained 37,000 W.B.C./c.mm., 80 per cent polymorphonuclear.

A sudden deterioration took place on 3.3.48, she became mentally confused and had a generalized convulsion. In the course of a few hours a complete right hemiplegia developed, with motor aphasia. The cerebrospinal fluid pressure was 300+ mm./water, and the fluid was normal. On 5.3.48 temperature was normal, and some power was returning in the right leg. On 6.3.48 blood examination showed 412,000 platelets per c.mm. Clotting time was normal. Steady improvement continued and by 19.4.48 there was only a very slight weakness in the right arm and right side of the face. Speech was a little hesitant. At no time was any pelvic abnormality detected.

Comment.—This patient had a septicæmic illness complicating the puerperium, during which symptoms and signs of cerebral venous thrombosis occurred. It is probable that the sagittal sinus was involved in addition to veins over the surface of the left cerebral hemisphere, in view of the greatly raised cerebrospinal fluid pressure. The high blood-platelet count is significant, and it is reasonable to assume that the same factors were operative in this case that result in venous thrombosis after uncomplicated childbirth.

Case 11.—A woman aged 32, thirty-six weeks' pregnant, was admitted to hospital on 15.2.48. Two weeks previously she had been treated for right frontal sinusitis and right otitis media by the administration of sulphathiazole. Three days before admission she complained of severe headache, and became drowsy. On the day before admission two fits took place. On examination she co-operated poorly, temperature was 101° F., pulse 90. There was no neck rigidity, and no tenderness over the frontal sinuses or mastoid processes. The ear-drums were normal. Early papillœdema was present, there was a left homonymous defect of the visual fields, and a left hemiparesis, more marked in the face and arm than in the leg. The cerebrospinal fluid was turbid and under a pressure of 300 mm./water. There were

10 R.B.C./c.mm. and 300 W.B.C./c.mm., 90 per cent polymorphonuclear. The total protein content was 90 mg. per cent and culture was sterile. Penicillin 100,000 units three-hourly was started.

In view of the meningeal reaction, it was considered that a frontal extradural abscess was likely to be present, and the patient was transferred to the National Hospital under the care of Mr. Harvey Jackson on 16.2.48. On the same day a live child was delivered by Cæsarean section under local anæsthesia. Further fits occurred, they were predominantly left-sided. On 18.2.48 the cerebrospinal fluid pressure was 160 mm./water, and the fluid contained 51 cells/c.mm., total protein 35 mg. per cent. Frontal burr holes were made on the same day. That on the left revealed normal cerebral cortex. On the right side the dura and arachnoid were thickened and the cortex appeared congested. Cortical biopsy showed acute œdema of grey and white matter. Fever settled by 3.3.48, and improvement commenced. Chemotherapy was continued. On 31.3.48, the patient was ambulant, and had only a mild spastic weakness of the limbs on the left.

Comment.—The final diagnosis of this patient's illness was cerebral thrombophlebitis following meningitis due to frontal sinus infection. The short history and fulminating onset with a moderate meningeal reaction suggested that extra- or sub-dural pus might be present, but the subsequent course of events showed this not to be so.

The fact that the patient was pregnant must be regarded as coincidental since the symptoms of venous occlusion started before delivery of child.

Diagnosis, Treatment and Prognosis

Of the 6 patients described it can be said that the diagnosis of cerebral thrombophlebitis could only be made with reasonable certainty at the onset in one instance (Case 5). In all the remainder some doubt existed as to the presence of intracranial suppuration, and the true diagnosis was only revealed by the subsequent course of events.

A study of the histories of these 6 patients shows that, with one exception, they had certain features in common which, upon reflection, assist in the diagnosis from cerebral abscess. In 5 patients the onset of cerebral symptoms was preceded by an acute infection of short duration (one to two weeks), the frontal sinus being the primary focus on three occasions. The cerebral symptoms were of sudden onset, usually with headache, followed by convulsions in turn followed by unilateral weakness, the whole picture developing in a matter of a few hours.

Cerebral abscess, unlike the condition described above, more often follows long-standing chronic suppuration of the middle ear or paranasal sinuses, and the cerebral symptoms are more often of insidious onset, and may not be fully developed for weeks or even months. Constitutional disturbance is often slight, and the cerebrospinal fluid may be normal, or show only a mild lymphocytic response.

It should, however, be emphasized that cerebral thrombophlebitis and cerebral abscess have common ætiological factors and could conceivably co-exist in the same patient. Further, a venous thrombosis due to infec-

tion forms an ideal starting point for an abscess which may only make its presence known some considerable time later. This latter event was demonstrated in the account of the second patient of this series. In the fourth patient described the onset of symptoms was fairly sudden, but followed protracted ill-health, and the longer history and insidious progress of hemiparesis were in favour of the presence of an abscess.

In conclusion it may be said that a diagnosis of cerebral thrombophlebitis may be made when a patient with a history of recent acute paranasal infection or otitis has convulsions followed by pareses; an acute meningeal reaction may be regarded as supporting the diagnosis. It must be borne in mind that the condition may precede or may co-exist with cerebral abscess formation, and failure of chemotherapy alone to bring about improvement should suggest the presence of added intracranial suppuration.

Little need be said of the treatment of this condition other than that the situation is one that calls for prompt and adequate chemotherapy. Anticoagulants do not appear to have any place in treatment as the thrombosis does not appear to have any great tendency to spread.

The primary source of infection may require surgical interference at the height of the illness but this appears to be exceptional.

No definite statement can be made in regard to prognosis since the introduction of penicillin is still relatively recent, but it can be said that the latter has converted a condition with a very high mortality into one in which the prospect of complete recovery is reasonably good.

Summary

Two series of patients are described in which a diagnosis of intracranial venous thrombosis was made.

In the first series of 5 patients the condition followed childbirth. This condition may be primarily thrombotic or may result from retrograde embolus from a pelvic thrombus. The points for and against these two hypotheses are discussed and the conclusion drawn that retrograde embolus, while anatomically possible, is physiologically most improbable, and that the intracranial thrombosis is primary and a result of local vessel damage during labour assisted by certain alterations in the circulating blood. Treatment with anticoagulant drugs is discussed.

In the second series 6 patients are described in whom cerebral venous thromboses were associated with local or general septic conditions. The difficulty of differentiation from cerebral abscess is considered, and the suggestion made that the acuteness of the primary infection together with the rapidity of onset of cerebral symptoms indicate the probability of thrombophlebitis rather than abscess formation.

The writer is indebted to the following for permission to publish details of certain of the patients in this paper: The Medical Committee of the National Hospital, Queen Square, Mr. Harvey Jackson, Mr. W. I. Daggett, Dr. E. B. Brooke, Dr. W. N. Rogers, Dr. R. B. McMillan, Dr. W. A. Pritchard, Dr. Ivor Balfour, and Dr. Heward Bell.

REFERENCES

ALPERS, B. J., and PALMER, H. D. (1929) *J. Nerv. and Ment. Dis.*, **70**, 465 and 606.
ASCHOFF, L. (1924) Lectures on Pathology, New York.
BATSON, O. V. (1940) *Ann. of Surg.*, **112**, 138.
BECK, D. K. (1944) *Proc. Roy. Soc. Med.*, **37**, 388.
BLAND, P. B., and GOLDSTEIN, L. (1932) *Am. J. Obst. and Gynæ.*, **23**, 815.
BRISTOWE, J. S. (1888) Diseases of the Nervous System, London, p. 184.
BRUSH, A. C. (1898) *Med. News*, **72**, 390.
CHURCHILL, F. (1854) *Dublin Quart. J. of Med. and Surg.*, **17**, 257.
COLLIER, W. (1891) *Brit. Med. Jour.*, **1**, 521.
DAWBARN, R. Y., EARLHAM, F., and HOWELL EVANS, W. (1928) *J. Path. and Bact.*, **31**, 833.
DICKENSON, LEE (1896) *Trans. Clin. Soc. Lond.*, **29**, 63.
GILLIGAN, D. R., and ERNSTEIN, A. C. (1934) *Am. J. Med. Sc.*, **187**, 552.
GOWERS, W. R. (1893) Diseases of the Nervous System, London, Vol. II, p. 450.
HAMILL, R. H. (1895) *Am. J. Obst.*, **32**, 106.
HÖSSLIN, R. v (1904) *Arch. Psychiat.*, **38**, 730.
HUNT, J. RAMSEY (1917) *Bull. Lying-in Hospital, N.Y.*, **11**, 73.
MARTIN, J. P. (1941) *Brit. Med. Jour.*, **2**, 537.
—— (1944) *Proc. Roy. Soc. Med.*, **37**, 383.
——, and SHEEHAN, H. L. (1941) *Brit. Med. Jour.*, **1**, 349.
MENIÈRE, P. (1828) *Arch. Gen. de Med.*, **16**, 489.
MYRICK, H. J. (1910) *Boston Med. and Surg. Jour.*, **163**, 764.
POUPON, C. (1885) *L'Encephale*, **5**, 393.
SALLÉS, J. (1913) Thèse de Paris.
SINCLAIR, M. A. (1902) *Lancet*, **2**, 204.
STANDER, H. J. (1945) Text Book of Obstetrics, New York.
STANSFIELD, F. R. (1942) *Brit. Med. Jour.*, **1**, 436.
SYMONDS, C. P. (1937) *Brain*, **60**, 531.
—— (1940) *Brit. Med. Jour.*, **2**, 349.
—— (1944) *Proc. Roy. Soc. Med.*, **37**, 386.
TAYLOR, JAMES (1899) In Allbutt's System of Medicine, London, Vol. VII, p. 574.
WRIGHT, H. P. (1942) *J. Path. and Bact.*, **54**, 461.

THE EFFECT OF THE INTRACISTERNAL INJECTION OF SALINE SOLUTIONS ON THE PRESSURE OF THE CEREBROSPINAL FLUID OF THE DOG

BY

T. H. B. BEDFORD

(From the Department of Pharmacology, Manchester University)

WEBSTER AND FREEMAN (1941), in a series of experiments on unanæsthetized dogs, found leucocytes in the cerebrospinal fluid at the end of nearly all experiments in which isotonic sodium chloride solution had been used to fill the manometer recording the pressure of the cerebrospinal fluid in the cisterna magna. A gradual rise in the pressure of the cerebrospinal fluid was generally found to accompany the pleocytosis. White cells were not found in the cerebrospinal fluid and the pressure remained unchanged in experiments where the cerebrospinal fluid was allowed to rise into the empty manometer. The use of a manometer previously filled with cerebrospinal fluid did not excite the appearance of leucocytes, but the cerebrospinal fluid pressure was found to be raised at the end of one experiment. The duration of their experiments is not stated, but, from a consideration of the records of related experiments, it appears to have been approximately five hours.

Bedford (1946) showed that the introduction of isotonic sodium chloride solution (0·9 gramme NaCl/100 c.c.) into the cisterna magna of dogs anæsthetized with "nembutal" (Abbott) generally caused polymorphonuclear leucocytes to appear in the cerebrospinal fluid, when the latter was examined five hours later, and that the introduction under the same conditions of distilled water was not followed by the appearance of reactive cells. In another series of experiments (Bedford, 1948), in which the animals, after initial anæsthesia with ether, were allowed to recover from the anæsthetic and to survive for a period of twenty-four hours, the introduction of both isotonic sodium chloride solution and of distilled water was followed by the appearance of polymorphonuclear leucocytes in the cerebrospinal fluid. The number of cells was, however, considerably greater after isotonic sodium chloride solution than after distilled water. Ringer's solution (Dale's formula) was found to be a less powerful irritant than isotonic sodium chloride solution, but significantly more so than distilled water.

In the experiments now reported, a study has been made of the effect on the pressure of the cerebrospinal fluid of the introduction of solutions of sodium chloride of different concentrations and a comparison has been

made with that of distilled water. The average duration of the experiments was six hours.

Experimental Procedure

The general experimental procedure was similar to that used in earlier experiments (Bedford, 1946, 1948). In this series of experiments, the dogs were anæsthetized with ether. The pressure of the cerebrospinal fluid was measured with a 1 mm. bore glass manometer. Readings were taken at intervals of three minutes until the cerebrospinal fluid pressure had attained equilibrium. The time required for this varied from ten to thirty minutes. The manometer was then detached and the cerebrospinal fluid contained within it retained for cytological examination. With the loss of as little cerebrospinal fluid as possible, the solution under investigation was introduced in the manner already described and, after withdrawal of the needle, the animal was allowed to recover from the anæsthetic. After an interval of six hours, the animal was again anæsthetized with ether and the pressure and the cell content of the cerebrospinal fluid determined. A strict aseptic technique was observed throughout these manipulations and the solutions were sterilized in alkali-free glass containers at a pressure of 12 lb. per square inch for twenty minutes. A constant volume (1 c.c.) of solution was introduced in all the experiments.

Results

The effect of ether anæsthesia.—Three dogs were anæsthetized with ether for three-quarters of an hour. This period exceeds the maximum duration of anæsthesia required during any subsequent experiment. The ether was administered by means of a pump through a catheter introduced into the trachea. An examination six hours later showed no significant change in the pressure of the cerebrospinal fluid and it remained free from reactive cells.

Table I.—The Effect of Simple Puncture and of Distilled Water on the Pressure and on the Cell Content of the Cerebrospinal Fluid

Simple Puncture				Distilled Water			
Wt. of dog in kg.	*Pressure of cerebrospinal fluid* — *Initial*	*Pressure of cerebrospinal fluid* — *After 6 hours*	*White cells per c.mm. C.S.F. after 6 hours*	*Wt. of dog in kg.*	*Pressure of cerebrospinal fluid* — *Initial*	*Pressure of cerebrospinal fluid* — *After 6 hours*	*White cells per c.mm. C.S.F. after 6 hours*
10·0	180	120	—	10·5	160	180	—
6·5	125	125	—	8·5	150	160	90
6·5	185	190	—	8·5	120	110	—
7·5	150	155	—	7·5	130	140	7
9·0	195	190	—	8·5	150	170	80
14·5	115	115	10	8·5	110	130	—
7·5	120	110	—	11·5	125	110	—
				14·0	140	140	—

TABLE II.—THE EFFECT OF THE INTRODUCTION OF SOLUTIONS OF SODIUM CHLORIDE OF DIFFERENT CONCENTRATIONS ON THE PRESSURE AND THE CELL CONTENT OF THE CEREBROSPINAL FLUID

0·9% NaCl				0·45% NaCl				1·8% NaCl				2·7% NaCl			
	Pressure of cerebrospinal fluid		*White cells per c.mm. C.S.F. after*		*Pressure of cerebrospinal fluid*		*White cells per c.mm. C.S.F. after*		*Pressure of cerebrospinal fluid*		*White cells per c.mm. C.S.F. after*		*Pressure of cerebrospinal fluid*		*White cells per c.mm. C.S.F. after*
Wt. of dog in kg.	*Initial*	*After 6 hrs.*	*6 hrs.*	*Wt. of dog in kg.*	*Initial*	*After 6 hrs.*	*6 hrs.*	*Wt. of dog in kg.*	*Initial*	*After 6 hrs.*	*6 hrs.*	*Wt. of dog in kg.*	*Initial*	*After 6 hrs.*	*6 hrs.*
9·5	140	220	3250	8·0	130	130	—	7·5	140	220	3500	7·5	130	170	2500
8·5	140	170	1400	11·0	150	160	—	8·5	130	150	3600	10·5	130	240	4000
6·0	80	220	3400	10·0	90	210	—	8·5	120	220	2500	13·0	180	260	2000
10·5	110	270	810	7·5	80	80	140	7·0	130	200	2100	10·5	130	260	5840
10·5	80	120	1070	6·5	70	80	300					15·0	170	230	7600
10·0	170	160	2100												
6·0	100	260	2200												
10·5	145	270	4500												
9·0	125	250	2300												
8·0	200	300	2500												
Mean		0·839	2353							0·524	2925			0·592	4388
±S.D.		±0·606	±1133							±0·280	±741			±0·315	±2336

For the purpose of determining S.D., the rise in the pressure of the cerebrospinal fluid has been expressed as a proportion of the initial pressure.

The effect of simple puncture and of distilled water.—The effect of simple puncture of the cisterna magna was studied in seven dogs. After introduction, the needle was allowed to remain in situ for twenty minutes. The needle was then withdrawn and the animal allowed to recover. The results obtained six hours later are summarized in Table I. It will be noticed that simple puncture was without significant effect on the pressure of the cerebrospinal fluid and that white cells were found at the end of one experiment only.

The introduction of distilled water was also without significant effect on the pressure of the cerebrospinal fluid. White cells were present at the end of three experiments out of a total of eight.

The effect of solutions of sodium chloride of different concentrations.—The effects of the introduction of sodium chloride in 0·9 per cent, 0·45 per cent, 1·8 per cent and 2·7 per cent concentrations are summarized in Table II. No significant difference was observed in the action of any of these solutions on the pressure or on the cell content of the cerebrospinal fluid. A significant rise in the pressure of the cerebrospinal fluid occurred in only one experiment after the introduction of 0·45 per cent NaCl and, in this instance, it was unaccompanied by pleocytosis. Leucocytes were found in two experiments out of a total of five. In both these experiments, there was no rise in the pressure of the cerebrospinal fluid and the number of cells per c.mm. of cerebrospinal fluid was considerably less than after the introduction of 0·9 per cent NaCl.

TABLE III.—THE EFFECT OF ISOTONIC GLUCOSE SOLUTION (5·4%) ON THE PRESSURE AND CELL CONTENT OF THE CEREBROSPINAL FLUID

Wt. of dog in kg.	*Pressure of cerebrospinal fluid*		*White cells per c.mm. after 6 hours*
	Initial	*After 6 hours*	
10·5	130	260	5,840
15·0	170	230	7,600
7·5	90	180	12,800
13·0	110	150	7,080
10·0	200	280	9,000
8·5	160	210	3,500
Mean ± S.D.		0·572 ± 0·333	7,637 ± 3,136

The effect of isotonic glucose solution.—A few experiments were performed with isotonic glucose solution (5·4 per cent glucose/100 c.c.). Glucose A.R. was used to prepare the solution, which was sterilized in the same way as the saline solutions. The pH of the solution before sterilizing averaged 5·4, and after sterilizing 4·2.

The results of the experiments are summarized in Table III, where it will be noticed that the effect on the pressure and the cell content of the cerebrospinal fluid did not differ significantly from that produced by the saline solutions. In all these experiments, including those with sodium chloride, the animals seemed normal in all respects at the time of terminal anæsthesia.

Discussion

It is evident, after a consideration of the results of the above experiments, that simple puncture of the cisterna magna and the introduction of 1·0 c.c. distilled water have no appreciable effect on the pressure of the cerebrospinal fluid when examined six hours later. White cells were found in the cerebrospinal fluid in one experiment only after simple puncture, and in three experiments out of a total of eight after the introduction of distilled water. The number of cells present was moderate in all instances. The introduction of 0·9 per cent, 1·8 per cent and 2·7 per cent NaCl and of 5·4 per cent glucose solution caused a marked rise in the pressure and the appearance of polymorphonuclear leucocytes in the cerebrospinal fluid. A study of the standard deviations of the means of the results of these experiments reveals no significant difference between any of these solutions on the pressure or on the cell content of the cerebrospinal fluid. The similarity of the results obtained after the use of different concentrations of sodium chloride was unexpected. It is interesting, however, that Weed (1935, 1936) and Bedford (1939) have shown that a solution of sodium chloride twice the isotonic strength is absorbed from the subarachnoid space at the same rate as isotonic solution, and that it is only when higher concentrations are used that a difference is observed. In view of the fact that no more than 1·0 c.c. of solution was introduced into the cisterna magna in the present experiments, it is probable that some degree of dilution took place immediately on introduction; the extent and rate of dilution would, of course, vary with different animals. It is noteworthy that, although a rise in the pressure of the cerebrospinal fluid was invariably associated with the presence of leucocytes in the cerebrospinal fluid, the reverse did not always obtain. The terminal pressure reading was actually lower than the initial in one instance after the use of 0·9 per cent NaCl solution, while in other experiments the rise in the pressure of the cerebrospinal fluid was moderate, although accompanied by a pronounced leucocytosis. The most probable explanation of this phenomenon is leakage from the original puncture hole in the cisterna magna. It has been possible on several occasions to demonstrate gross leakage from the puncture hole, even after the use of a needle of relatively small calibre and the exercise of care to avoid disturbing the needle when inserted. Not only may a

leaking puncture hole allow the escape of cerebrospinal fluid into the extrathecal tissues, but blood and tissue fluids may be aspirated from this region into the subarachnoid space when the intracisternal pressure is low, as occurs in the "head-up, tail-down" posture. This can readily be demonstrated in animals with a leaking puncture hole by the use of a suspension of Indian ink.

It remains to consider the possible bearing of the above findings in relation to current clinical procedure. The introduction into the cisterna magna of 0·9 per cent and higher concentrations of NaCl invariably provoked the appearance of leucocytes, and generally caused a rise in the pressure of the cerebrospinal fluid. The volume of solution introduced was 1·0 c.c.; this would correspond in the human subject to the introduction of about 7·0 c.c. of solution. Considerably larger volumes than this are not infrequently introduced into the human subarachnoid space. The relatively slight irritant action of 0·45 per cent NaCl is interesting. The experiments would seem to provide strong evidence that solutions of drugs required for introduction into the subarachnoid space are best made up with distilled water, rather than rendered isotonic by the addition of sodium chloride. Before this conclusion is, however, accepted in its entirety, it would seem desirable to have some knowledge regarding the immediate effect of the introduction of saline solution and of distilled water on the normal functioning of the central nervous system. Experiments are now in progress to determine the effect of intracisternal injection of these solutions on respiratory rhythm and on systematic blood-pressure.

Summary

A study has been made of the effect of the introduction into the cisterna magna of the dog of solutions of sodium chloride on the pressure and on the cell content of the cerebrospinal fluid. The duration of each experiment was six hours. The introduction of 0·9 per cent, 1·8 per cent and 2·7 per cent NaCl and of 5·4 per cent (W/V) glucose solution caused a marked rise in the pressure and the appearance of polymorphonuclear leucocytes in the cerebrospinal fluid. No significant difference was observed in the action of any of these solutions on the pressure or on the cell content of the cerebrospinal fluid. The introduction of 0·45 per cent NaCl solution caused a rise in the pressure of the cerebrospinal fluid in one experiment out of a total of five; a moderate number of leucocytes were present in two experiments but there was no associated rise in the pressure of the cerebrospinal fluid.

Simple puncture of the cisterna magna and the introduction of distilled water were not followed by a rise in the pressure of the cerebrospinal fluid. Polymorphonuclear leucocytes were found in three experiments

out of a total of eight after distilled water, but the number of cells present was considerably less than after the introduction of the saline solutions. The possible significance of these findings in relation to current clinical practice is discussed.

REFERENCES

BEDFORD, T. H. B. (1939) *J. Physiol,* **96**, 392
—— (1946) *J. Physiol.,* **104**, 299.
—— (1948) *Brit. J. Pharmacol.,* **3**, 80.
WEBSTER, J. E., and FREEMAN, N. E. (1941) *Ann. Surg.,* **113**, 556.
WEED, L. H. (1935-6) *Amer. J. Physiol.,* **114**, 40.

THE COPPER AND IRON CONTENT OF BRAIN AND LIVER IN THE NORMAL AND IN HEPATO-LENTICULAR DEGENERATION

BY

J. N. CUMINGS

(From The Clinical Pathological Department, National Hospital, Queen Square, London)

DETERMINATIONS of the copper content of brain and liver have been made by few workers, but recently increased interest has been shown in copper in relation to certain demyelinating diseases. This paper describes the results of copper and iron estimations in different parts of the cerebrum and in the liver, both in normal subjects and in some pathological conditions, with special reference to hepato-lenticular degeneration.

The Copper and Iron Content of Normal Adult Brain and Liver

Bodansky (1921) estimating copper in whole wet brain found 0·36 to 0·6 mg./100 grammes and Tompsett (1935) 0·216 to 0·484 mg./100 grammes, while Eggleton (1940) obtained a figure of 1·81 mg./100 grammes for whole dry brain. Tompsett in wet liver found 0·296 to 0·909 mg./100 grammes of copper, while in dry liver Buckwald and Hudson (1944) found 0·75 to 8·15 mg./100 grammes, Eggleton 1·53 to 9·99 mg./100 grammes, Gross *et al.* (1942) 1·4 to 4·5 mg./100 grammes and Gillman *et al.* (1945) 2 to 17 mg./100 grammes.

Tompsett obtained figures of 0·4 to 1·48 mg./100 grammes of iron in whole wet brain and Wuth (1923) found 46·02 to 63·35 mg./100 grammes by dry weight in the globus pallidus. Tompsett in wet liver found 2·77 to 16·24 mg./100 grammes. Dry liver contained 21·6 to 427·0 mg./100 grammes according to Buckwald and Hudson, while Gillman *et al.* obtained an average of 30 mg./100 grammes and Gross *et al.* found 17·2 to 81·4 mg./100 grammes.

Copper and Iron in Hepato-Lenticular Degeneration and in Cirrhosis of the Liver

Gillman *et al.* in dry pigmented cirrhotic livers obtained a copper content of 42 mg./100 grammes and an iron content of 2,630 mg./100 grammes, whereas in a dry, non-pigmented cirrhotic liver, the figures were 6 mg./100 grammes and 30 mg./100 grammes respectively. Haurowitz (1930) in two cases of Wilson's disease found the copper content of the livers to be 5·9 and 4·8 mg./100 grammes, and an iron content in one case of 53 mg./100 grammes. He also gave figures of 2·8 and 3·1 mg./100 grammes for copper and 8·0 and 10·5 mg./100 grammes for iron in the basal ganglia. Glazebrook (1945) in one case of Wilson's disease found 4·6 mg./100 grammes of copper in the liver and in the basal ganglia and cortex 1·275 and 0·781 mg./100 grammes respectively. The figures of the last two authors are presumably related to wet weight of tissue.

EXPERIMENTAL

Method.—Liver and brain from normal subjects, from cases of obstructive jaundice, multilobular cirrhosis of the liver and of hepato-lenticular degeneration, obtained at post-mortem, were placed in specially cleaned glass jars or Petri dishes.

Portions of the areas chosen from these tissues were cut into small fragments with glass spatulas specially ground so as to cut. The tissues were weighed, and re-weighed after drying at 105° C. until a constant weight had been obtained. The water content of the tissues was then calculated.

A suitable amount of each tissue was ashed in a silica crucible at 450° C. and the copper content was estimated, using the sodium diethyldithio-carbamate method, essentially similar to that described by Eden and Green (1940). The iron content was also estimated on an ashed sample according to the method of McCance and Shipp (1933).

Reagent blanks were included in the estimations in order to check that no copper or iron was present in these, and considerable care was exercised in cleaning glassware and crucibles, which were kept specially for these estimations. No metal instruments, such as crucible tongs and scalpels, were used. All amounts of copper and iron have been calculated on dry weight of tissue.

Results

Normal tissue.—(a) Brain: Originally 27 brains were examined for the copper content of cerebral grey and white matter and these yielded an average figure of 3·06 mg./100 grammes (range 1·2 to 8·2 mg./100 grammes), for white matter, and an average of 3·33 mg./100 grammes (range 1·1 to 7·2 mg./100 grammes), for cortical grey matter.

Six normal brains were then examined in more detail for copper and iron and Table I shows the results.

(b) Liver: Copper and iron were estimated in 9 normal livers and the figures are included in Table I.

Table 1.—Range of Copper and Iron Content in Normal Tissues (Dry)

Tissue	*Water %*	*Cu. (mg./100 grammes)*	*Fe (mg./100 grammes)*
Cortical white matter	67·46 - 72·35	1·1 - 8·2	26·9 - 50·7
	(M 70·46)	(M 3·3)	(M 33·3)
Cortical grey matter ...	79·77 - 87·91	2·4 - 9·9	32·8 - 46·1
	(M 83·46)	(M 6·2)	(M 38·8)
Caudate	83·21 - 83·98	3·4 - 9·4	50·4 - 65·2
	(M 83·51)	(M 7·06)	(M 56·2)
Thalamus	65·5 - 83·15	3·1 - 12·4	31·2 - 50·0
	(M 77·88)	(M 5·9)	(M 41·4)
Putamen	78·92 - 81·12	6·1 - 12·0	36·1 - 94·5
	(M 80·27)	(M 9·3)	(M 70·3)
Globus pallidus ...	74·0 - 76·6	10·5 - 18·8	73·5 - 172·0
	(M 75·4)	(M 14·9)	(M 112·9)
Liver	62·3 - 75·48	3·7 - 17·2	25·0 - 180·0
	(M 72·6)	(M 10·7)	(M 103·0)

M is the average of the estimations.

Abnormal conditions.—It was thought that jaundice or multilobular cirrhosis of the liver might show an altered copper and iron content in the brain and liver and one case of each of these conditions was examined and Table II shows the results obtained.

TABLE II.—COPPER AND IRON CONTENT IN JAUNDICE AND CIRRHOSIS OF THE LIVER

	Jaundice			*Cirrhosis*		
Tissue	*Water*	*Cu*	*Fe*	*Water*	*Cu*	*Fe*
Cortical white matter	70·17	2·9	19·6	75·54	3·7	19·8
Cortical grey matter	83·74	4·6	51·1	86·1	9·3	54·0
Caudate	80·48	4·2	35·0	84·8	6·1	51·7
Thalamus	85·12	3·3	29·2	82·5	10·1	39·2
Globus pallidus and putamen	79·06	9·8	76·1	81·56	8·8	67·6
Liver	66·59	7·3	58·6	70·95	20·3	247·8

Water in per cent, copper and iron in mg./100 grammes of dry tissue.

It will be seen that, in cirrhosis, the liver shows a little more copper and more iron than the normal controls, while there is very slightly less iron in the cerebral white matter than in the normal. The case of jaundice, which was the result of a carcinoma in the head of the pancreas, gave figures which were within normal limits, except that there was very slightly less iron in the cortical white matter.

Material from 3 patients suffering from hepato-lenticular degeneration, verified by histological examination, was also examined and the results are to be found in Table III.

TABLE III.—COPPER AND IRON CONTENT IN HEPATO-LENTICULAR DEGENERATION

	Water			*Cu*			*Fe*		
Tissue	*Case* 1	*Case* 2	*Case* 3	*Case* 1	*Case* 2	*Case* 3	*Case* 1	*Case* 2	*Case* 3
Cortical white matter	69·3	70·5	70·0	10·9	14·7	12·9	32·3	62·0	43·7
Cortical grey matter	83·36	82·3	84·6	4·6	27·6	46·5	70·5	108·0	103·9
Caudate	82·6	79·1	83·95	10·1	31·8	13·8	134·6	109·0	107·3
Thalamus	79·14	83·1	78·0	31·9	20·7	31·9	67·1	156·0	100·2
Putamen	—	81·0	84·9	—	60·5	69·3	—	99·3	75·0
Globus pallidus ...	78·52	—	79·3	8·4	23·0	39·9	126·1	131·3	113·6
Liver	77·46	76·2	78·39	156·4	55·0	39·4	71·6	70·7	69·5

Water in per cent, copper and iron in mg./100 grammes of dry tissue.

DISCUSSION

Copper.—The results which have been recorded here show that, although in the normals there is some variation in the amount of copper in the liver and in different parts of the cerebrum, yet there is a considerable retention of copper in the tissues in patients suffering from hepato-lenticular degeneration. Thus in the liver there is at least a four-fold increase, and in one case the amount of copper found was fifteen times the normal. It has been shown that neither in the case of jaundice nor in the case of multilobular cirrhosis was there a similar degree of retention. The amount of copper in the liver in the normal controls is much the same as that found by other workers.

The copper content of normal brain has been rarely examined, and

when so examined it was in relation to the whole brain except that Tingey (1937) examined a number of separate areas of the normal brain both for copper and for iron. He obtained figures which were slightly lower than those shown here. He found 0·29 mg. of copper in 100 grammes of fresh white matter, 0·41 mg. for the same amount of fresh thalamus, and 0·6 mg. for the pallidum, but he did not give the water content of these brains. His figures for iron, recorded on dry tissue in white matter, corpus striatum and cortex are 12·6, 55·5 and 22·6 mg./100 grammes respectively, but in general the figures Tingey obtained are within the range of the figures found in this investigation.

The brain in hepato-lenticular degeneration is seen to contain considerably more copper than the normal. This is particularly true of the globus pallidus and the pûtamen, this last area being markedly affected in the disease, but it is also noticeable that in the cortical white and grey matter there is a definite though less marked increase. The amounts found in these three cases are even greater than those recorded by Haurowitz and by Glazebrook. It is of interest to note that cases 2 and 3 of hepato-lenticular degeneration were respectively sister and brother aged 20 and 17 years. Case 1 was an older man aged 46 years, and it may be that the higher concentration of copper in the liver in this case is directly related to this difference in age. All three showed the typical Kayser-Fleischer eye feature, typical liver cirrhosis and the cerebral changes seen in this disease.

Mallory (1925) in his animal experiments produced necrosis of liver cells and cirrhosis as a result of copper administration. However, in the liver in cases of hæmochromatosis he found no more copper than in the liver of normal controls, but he associates this condition with copper and alcohol since more than half of his cases gave a history of intimate contact with copper in one form or another. Gillman *et el.* investigating cases of pigmented cirrhosis which were practically identical with hæmochromatosis, found an increased copper content in the liver but they found no such increase in the livers of patients suffering from non-pigmented multilobular cirrhosis.

Mandebrote *et al.* (1948) working on the relationship of copper to demyelinating diseases found in one case of hepato-lenticular degeneration a raised urinary output of copper, and further they found that BAL produced a very considerable increase in such excretion. It would seem rational, therefore, that in the early stages of hepato-lenticular degeneration BAL might be administered as a diagnostic procedure. It might also be used in an attempt to reduce the copper content of the liver and brain, and possibly thereby to prevent further damage to the tissues.

Iron.—It is seen that the cases of hepato-lenticular degeneration

recorded here show rather less iron than is commonly seen in the normal liver. The basal ganglia and the cortical grey matter contained rather more iron than in the normal control. Haurowitz found rather less iron in the brains and the livers of his cases than in those recorded above.

Sheldon (1927-8) in a detailed examination of a case of hæmochromatosis found a considerable increase of iron in the liver, and some increase of iron in the putamen, basal ganglia and cortical white and grey matter. Gillman *et al.* in the liver of cirrhosis of Type 4, which is practically indistinguishable from that of hæmochromatosis, also found a considerable increase of iron together with some increase of copper. The cases of hepato-lenticular degeneration showed no increase of iron in the liver even though there was some increase of iron in the caudate, thalamus and cortical grey matter. There was, however, no increased iron in the putamen, which with the lower iron content in the liver are in sharp contrast to the findings of Sheldon in his case of hæmochromatosis. Gillman *et al.* considered that their cases of hæmochromatosis were the result of malnutrition, while Sheldon considered the condition a result of an inborn error of metabolism, a view that is now widely held. Hepato-lenticular degeneration appears to differ, in that in this condition there is a retention of copper, with some alteration of iron content, in some parts of the body. By analogy it would also seem possible that hepato-lenticular degeneration is an inborn error in mineral metabolism. There is no definite evidence as yet to suggest that the cirrhosis is caused by the deposition of copper in the liver.

SUMMARY

Copper and iron estimations have been made in the liver and in various parts of the brain in hepato-lenticular degenerations and these have been compared with the results of similar estimations in normal subjects, and in case of jaundice and of multilobular cirrhosis.

There has been shown to be a considerable retention of copper in these tissues in hepato-lenticular degeneration. The possibility that the condition is a metabolic disorder similar to that of hæmochromatosis has been discussed.

I wish to express my thanks to Dr. Macdonald Critchley and Dr. Denis Brinton, under whose care were the patients, to Professor W. D. Newcomb, Dr. W. Blackwood and Dr. D. P. King for obtaining some of the post-mortem specimens, and to Mr. H. J. Goodwin for technical assistance.

REFERENCES

BODANSKY, M. (1921) *J. Biol. Chem.*, **48**, 361.
BUCKWALD, K. W., and HUDSON, L. (1944) *Cancer Research*, **4**, 645.
EDEN, A., and GREEN, H. H. (1940) *Biochem. J.*, **34**, 1202.
EGGLETON, W. G. E. (1940) *Ibid.*, **34**, 991.

GILLMAN, J., MANDELSTAM, J., and GILLMAN, T. (1945) *S. Afr. J. Med. Sci.*, **10**, 109.
GLAZEBROOK, A. J. (1945) *Edin. Med. J.*, **52**, 83.
GROSS, H., SANDBERG, M., and HOLLY, O. M. (1942) *Amer. J. Med. Sci.*, **204**, 201.
HAUROWITZ, F. (1930) *Zeit. Physiol. Chem.*, **190**, 72.
MCCANCE, R. A., and SHIPP, H. L. (1933) The Chemistry of Flesh Foods and their Losses on Cooking, M.R.C., S.R.S., **187**, 39.
MALLORY, F. B. (1925) *Amer. J. Path.*, **1**, 117.
MANDELBROTE, B. M., STANIER, M. W., THOMPSON, R. H. S., and THRUSTON, M. N. (1948) *Brain*, **71**, 212.
SHELDON, J. H. (1927-8) *Quart. J. Med.*, **21**, 123.
TINGEY, A. H. (1937) *J. Ment. Sci.*, **83**, 452.
TOMPSETT, S. L. (1935) *Biochem. J.*, **29**, 480.
WUTH, O. (1923) *Zeit. f.d.ges. Neurol. and Psych.*, **84**, 474.

ON A POSSIBLE RELATIONSHIP BETWEEN HEREDITARY ATAXIA AND PERONEAL MUSCULAR ATROPHY; WITH A CRITICAL REVIEW OF THE PROBLEMS OF "INTERMEDIATE FORMS" IN THE DEGENERATIVE DISORDERS OF THE CENTRAL NERVOUS SYSTEM

BY

MARTIN ROTH

(*From the Maudsley Hospital*)

In the borderlands between the heredo-familial disorders of the central nervous system commonly recognized as distinct clinical entities there are intermediate clinico-pathological forms which make classification of these disorders a difficult task and raise many important problems. In particular, the existence of such hybrid forms raises the question of possible factors which are common to the diseases apparently combined in them.

In this paper, two families are described. In the first Charcot-Marie-Tooth disease occurred together with one example of abortive Friedreich, abnormalities that would fall into the group described by Roussy and Levy, and early disabilities in children that may develop into any of these. The second family contained one case in which the Friedreich syndrome was associated with the amyotrophy typical of peroneal muscular atrophy. The patient also exhibited some features more commonly associated with the so-called "Marie" type of ataxia and suffered from epilepsy, a condition rarely recorded in this group of disorders. Her mother exhibited signs suggestive of an abortive form of Friedreich's disease.

An attempt will be made to apply some modern genetic concepts to the problems raised by the existence of these intermediate forms and of pedigrees containing different clinical syndromes.

We are mainly concerned in this paper with cases on the borderlands of Friedreich's disease and peroneal muscular atrophy, although their problems are those of transitional and abortive forms in general.

The published reports may be divided into the following principal groups:—

(*a*) Cases and genetic evidence suggesting a connexion between Friedreich's disease, Marie's cerebellar degeneration (spastic ataxia) and spastic paraplegia. There have been many accounts of families with both the Friedreich and Marie syndromes (Raymond, 1905; Bauer and Gy, 1909; Wutscher, 1910; Frey, 1912) and of intermediate forms (Perrera, 1906; Söderbergh, 1910). Links between hereditary ataxia and familial spastic

paraplegia have been suggested for a considerable time (Ballet and Rose, 1905; Raymond and Rose, 1906, &c.). The work of Bell and Carmichael (1939) on the genetics of this group showed that the three syndromes were closely related, although the relationship proved a complex one.

(*b*) Intermediate forms and pedigrees suggesting a relationship between Friedreich's disease and peroneal muscular atrophy. (Spiller, 1910; Biemond, 1928; Galliotti, 1928). The status of families in which abortive forms only were prevalent (Roussy and Levy, 1926; Symonds and Shaw, 1926; Rombold and Riley, 1926; Popow, 1932; van Bogaert and Borremans, 1932, &c.) has been in dispute, some authors linking them to the Friedreich group, others allocating them to the Charcot-Marie-Tooth syndrome. Spillane's interesting family (1940) showed that peroneal muscular atrophy, Friedreich's disease and an abortive amyotrophic disorder, could all result from the expression of the same gene.

(*c*) A small group of cases suggesting links between Friedreich's disease and the myopathies. (Bing, 1905; Ghilarducci, 1906; Jastrowitz, 1911; Werthemann, 1927.)

(*d*) Some isolated cases suggesting links between Friedreich's disease and Leber's hereditary optic atrophy (Pines and Tron, 1925; Ferguson and Critchley, 1928).

(*e*) A group of families in which, associated with the main disease or appearing in otherwise unaffected members of the family, there were observed a number of abnormalities including mental defect, congenital heart disease, psychopathy, diabetes, epilepsy, deafness, minor deformities of various sorts, &c. The occurrence of these defects has been so often recorded in pedigrees of Friedreich and peroneal muscular atrophy that their association with the fully-fledged neurological syndrome is unlikely to have been a fortuitous one (cf. the family studied by Rütimeyer in 1883 and later investigated by Frey in 1912 and Klein in 1937, and also that published by Curtius, Störring and Schönberg in 1935).

From the point of view of the genetic problems raised by them, the cases in the literature may be divided into three principal categories, raising problems which are related but not identical.

(1) Clinical syndromes, usually considered distinct, occurring in the same family or combined in one or more individual cases in a family—or both phenomena together in one pedigree.

(2) Abortive forms either (*a*) associated with the fully-fledged syndrome in the same family or (*b*) breeding true, only the attenuated form occurring through several generations.

(3) Families with a wide distribution of abnormalities not confined to the central nervous system.

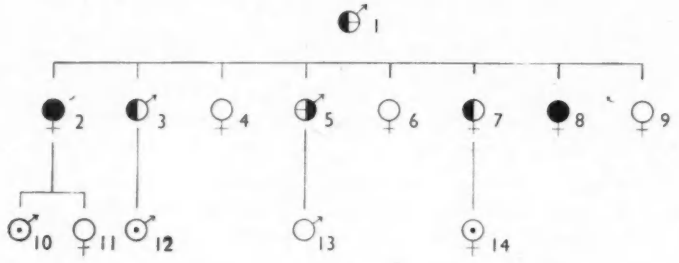
We shall have occasion to refer to these three groups in our discussion.

Case Reports

We shall describe two families which offer suggestions similar to those of Biemond, Spillane, &c.

Family I.—Mother, aged 64. Examined and found normal except for some chronic bronchitis. She and Case 8 were informants about other members unwilling to be examined. No consanguinity.

Fig. 1. — Family I.



● = Charcot-Marie-Tooth's disease

◐ = Abortive Charcot-Marie-Tooth (except 2, who is an example of the fully-fledged syndrome)

◑ = Abortive Friedreich

⊙ = Incipient disease

⊕ or ⊕ Psychopathic personality

Note: 3 suffers from duodenal ulcer, 5 suffered with this for several years and died of pyloric stenosis, 6 died from mitral stenosis, 2 is also a psychopathic personality

Case 8.—Aged 27. Development normal until left foot became highly arched and toes curled up when aged 9. A year later right foot became similarly deformed. She now had difficulty in getting up stairs, as feet felt "heavy" and toes tended to catch on the steps, and in rising from squatting position. Plastic operations when aged 12 and 17 made disability worse. After the first operation unable to raise feet, which also became everted as she walked. Legs began to waste at 12. Six to seven years ago wasting and weakness extended to muscles above knees and has advanced slowly since. For ten years there has been slowly progressive wasting of her hands. In recent years frequent sensations in arms and legs, and throbbing pain in soles of feet.

Examination.—Healthy looking, intelligent girl. Could walk slowly and laboriously with aid of irons, but unable to stand without them. In standing assumed an attitude of lordosis with the trunk thrown backwards in a manner reminiscent of pseudo-hypertrophic muscular dystrophy. Cranial nerves normal. No nystagmus. Speech and articulation unaffected. Upper limbs poorly developed and hypotonic. Severe wasting of intrinsic muscles of both hands with pronounced "main en griffe" deformity. (Nevertheless remarkably agile with hands, being

able to write legibly, knit, sew, do up buttons, but easily fatigued.) Generalized wasting of forearms with weakness of flexion and extension, especially latter at both wrists. Wasting and weakness worse on left side. No fibrillation. Co-ordination good and sensation normal. In the trunk no bony deformity apart from lumbar lordosis. Unable to sit up from lying down position without using fists. Feet short and stumpy with high inner arches and clawed toes. Original deformity obscured by the multiple operation scars. Almost total paralysis of dorsiflexion and no voluntary movement in toes. Slight plantar flexion of foot possible. Severe symmetrical wasting of all muscles below knees, especially in peronei and anterior tibials. Lower third of both thighs wasted, producing typical "inverted champagne bottle" appearance of lower limbs. Quadriceps weak. All movements at the hip joints weakened, especially extension. No cerebellar signs. Superficial sensation slightly blunted over lower third of legs and feet. Postural sense in the toes and vibration sense in lower parts of legs considerably impaired. All deep reflexes absent. Abdominal reflexes normal, but no plantar responses. In spite of severe disabilities, which she bore with fortitude, she led a richly active life, doing her own housework, encouraging other disabled members of her family. Apart from depression for some weeks following her operation at 17 her mood was stable.

There seemed to be no alternative to a diagnosis of Charcot-Marie-Tooth disease in this case. Absence of thickened nerve trunks and severe sensory impairment excluded hypertropic interstitial neuritis.

Case 1.—Male, died at 66 in 1941. Throughout life he had had a heavy, clumsy, broad-based gait. Well known in the family to have had the high-arched clawed foot exhibited by several of his children. He was a man of totally unpredictable moods and violent temper. His behaviour towards his family was cruel, selfish and irresponsible. He left home in 1937 for no apparent reason, never to return. He had had six sisters and three brothers, one of the latter a non-identical twin. They lived in Europe and America and no reliable information could be obtained about them.

Case 2.—Female, aged 42. Seen but not examined. She suffers from a pes cavus deformity of the feet and has been diagnosed as a case of Charcot-Marie-Tooth disease by several neurologists. Her disability commenced at about the age of 24 with a clumsy gait and a tendency for her feet to turn outwards in walking. It has never been severe and underwent slow improvement until a pregnancy seven years ago, when she developed massive œdema of her legs (subsequent investigation revealed that she had polycystic kidneys). Her gait has since become gradually more clumsy and now has a definite high steppage quality with a wide base. One of her children is affected (Case 10), but the other has so far shown no abnormality. She is an emotionally unstable individual whose prevailing mood is one of depression and chief subjects of conversation, sickness and death. She has always been subject to violent aggressive outbursts.

Case 3.—Male, aged 39. He has a mild pes cavus deformity which has not caused disability. His growth and development were normal and he does not know when the deformity developed. The tendon reflexes of both lower limbs are absent. Plantar responses are flexor. No cerebellar signs or scoliosis. He is shy and apprehensive, subject to long bouts of tension and anxiety and preoccupied with his mild abnormality. He is kindly and affectionate and attached to the family. He has suffered from a duodenal ulcer for some years.

Case 4.—Female, aged 38. Not seen. Has no disability and medical examinations by several practitioners have not revealed abnormal physical signs.

Case 5.—Male, aged 35, when he died of pyloric stenosis in 1945. He had never had difficulty with walking or speech. Seen eighteen months before his death in 1945 he was found to have well-marked nystagmus on lateral deviation

to either side, dorsal scoliosis, a mild but definite pes cavus deformity of the feet, and absent knee and ankle jerks. Plantar responses were flexor. There was coarse tremor of the outstretched hands not aggravated on volition. He was a vain, egotistical individual, with a violent destructive temper, feared by the family. If his requests were not immediately satisfied he was liable to smash crockery and furniture in a fit of rage. At school he was backward and made attacks on other boys. Was diagnosed as suffering from duodenal ulcer about five years before his death, but was incapable of keeping to a diet for longer than a few weeks, and would indulge in orgies of overeating. Both the occasions on which his ulcer perforated were preceded by periods of weeks during which, according to his family, he ate enormous meals. He finally died of pyloris stenosis. In view of the nystagmus, scoliosis, and pes cavus, as well as absent knee and ankle jerks, this case was regarded as an abortive Friedreich.

Case 6.—Died at 20, 11 years ago, from heart failure due to mitral stenosis. She had no abnormality of her feet or any difficulty in walking.

Case 7.—Female, aged 29. Not examined. Feet became arched and the toes clawed at about 17. Her gait became stiff and broad-based. Her disability did not progress until she was 26 when she became a little more clumsy. She sought medical advice and was told she was suffering from a mild form of "the family disease"—peroneal muscular atrophy. She is only very slightly disabled at present and the condition has not progressed appreciably in the past three years. She is said to be emotionally unstable and unpredictable in conduct, and has occasional temper outbursts.

Case 9.—Female, aged 25. Seen but not examined. She has never had any difficulty with walking or foot deformity. No anomalies of personality.

Case 10.—Female, aged 16. Not seen. Daughter of Case 8. At 10 she began to develop arched stumpy feet and curled-up toes. They have became gradually worse. She now has severe pes cavus deformity. Orthopædic advice has been sought, but parents have been told nothing could be done. Her gait is heavy and clumsy.

Case 11.—Male, aged 6. Not seen. Suffers from asthma. No other abnormality noted so far.

Case 12.—Male, aged 3½. Not seen. Is said to have been walking in a stiff and clumsy manner recently. Has no pes cavus.

Case 13.—Male, aged 1 year 2 months. So far no abnormality noted.

Case 14.—Female, aged 3½. Not seen. Recently right leg has been noted to turn outwards when walking. This abnormality is inconstant and she has no pes cavus.

Cases 10 and 11 are said to have always exhibited marked temper tantrums. Behaviour disorders were described in Cases 12 and 14.

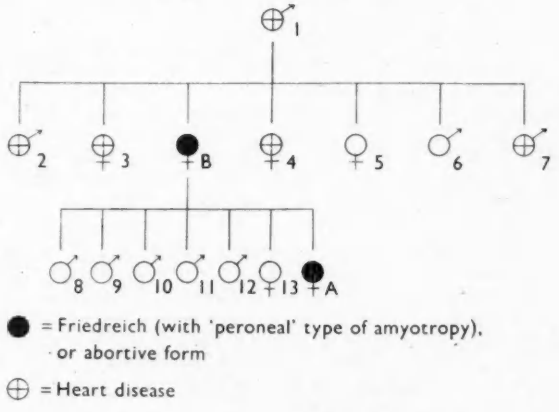
FAMILY II.—The informants were the propositus and her mother. Father reported normal until death from pneumonia. No history of consanguinity.

Case A (Propositus).—Early development uneventful. Personality before illness normal. At 18 she fractured her clavicle. Six months later she had a pain in the chest. X-rays showed right pleural effusion with slight apical infiltration. After six months in a sanatorium, where she was afebrile, she returned home in good health. In March 1945 she had three major fits at 24-48 hour intervals. She discharged herself in a week after she had been put on anticonvulsants. For the next four to five months she had "funny dizzy feelings" every one to two weeks, but was free from them towards the end of 1945. In the spring of 1946 she began to stagger in walking, her speech became slurred and two to three months afterwards her hands

clumsy. Her fits grew more frequent following news of her husband's death in July 1946, and her clumsiness and speech became worse in subsequent months. On December 1 she went into status epilepticus and was admitted to hospital after twenty-four hours' unconsciousness. She recovered eight hours later. Her speech was then noted to be markedly slurred and all her limbs greatly weakened. When she was being transferred to the Maudsley Hospital on 20.12.46 she found she was unable to walk and could stand only with support.

Examination.—Her appearance was rather youthful for her years. Her prevailing mood in the first week following admission was euphoric. She wore a fatuous smile and readily burst into fits of laughter. There was considerable lability, bouts of weeping coming suddenly in response to inadequate stimuli. She showed defective grasp of the seriousness of her disability. She was fully orientated, attention and concentration were normal, and co-operation good. No physical abnormality outside central nervous system.

Fig. 2. — Family II.



Central nervous system.—No aphasia. Articulation drawling, slurred and explosive with some tendency to overaction of muscles of lips and jaw. Slow coarse titubating tremor of head. Marked pallor of both optic discs. Vision: right 6/6, left 6/9. Pupils reacted normally. Well-sustained cerebellar nystagmus on deviation to both sides, more marked to left. Hearing normal and results of vestibular stimulation within normal limits. Upper limbs markedly hypotonic. Severe wasting of thenar and hypothenar eminences and interossei, with slight "en griffe" deformity of hands. Intrinsic muscles all weak, but the long flexors and extensors of thumb comparatively spared. Weakness of flexion, extension, supination and pronation at the wrist and of the long extensors of the fingers. Moderate weakness of flexion at the elbow. No fibrillation. Well marked swaying of outstretched upper limbs with gross intention tremor, dysmetria, dysdiadochokinesis, and rebound phenomenon equal on the two sides. There was a dorsal kyphoscoliosis with the kyphotic deformity most pronounced. During respiration, some asynergy between thoracic and diaphragmatic movement. Lower limbs hypotonic and pes cavus deformity present in both feet with "Friedreich" position of the toes. Feet, legs, and lower parts of thighs markedly wasted, with typical "inverted champagne bottle" appear-

ance of lower limbs. Coarse fasciculation in extensors of the wrists and peronei. Movements at hip-joints normal. Gross weakness in quadriceps and hamstrings, dorsiflexion of feet almost absent and of the toes severely weakened; eversion and plantar flexion also very weak.

In the legs the wasting most marked in peronei and anterior tibials, while in thighs the quadriceps were most affected. Gross inco-ordination of cerebellar type in both lower extremities. Sensation was normal except for impaired postural sense in right toes and diminished vibration sense in lower thirds of both legs. Knee-jerks, slight flickers only, triceps-jerks diminished, other deep reflexes absent. Abdominal responses absent in upper quadrants, diminished in lower. Plantar responses both extensor.

Investigations.—C.S.F. pressure 100 mm. No Block. Protein 30 mg. per cent. Cells less that 1 per c.mm. W.R. and Kahn negative. X-rays of skull and cervical spine normal. X-ray of chest showed small healed foci at both apices. Blood-count and B.S.R. normal. E.E.G. studies showed a gross, generalized abnormality with bilaterally synchronous paroxysmal high-voltage delta activity, most prominent in the frontal regions. Frequencies of the theta band were also prominent throughout. There was a suggestion in the earlier records of a phase reversal in the right temporo-occipital area, but no definite focus located. Later records failed to show this last abnormality. Apart from this fleeting focus, no significant asymmetry in any record. Records taken some time after a fit had taken place showed marked reduction in delta activity, but repeated paroxysmal outbursts of slow waves with reduced voltage were still seen.

Progressive Matrices: Grade V. Wechsler I.Q.75 (with no appreciable discrepancy between scores in sub-tests). Shipley-Hartford test for deterioration invalid, owing to low vocabulary score. There was thus no clear evidence of intellectual deterioration. Her I.Q. placed patient in the lowest 10 per cent of the population with respect to intelligence.

Progress.—There was no change in patient's neurological condition during stay in hospital. She had major epileptic attacks about once a week, preceded by an hour of symmetrical twitching movements of hands, arms and face. In this period she was often in a state of clouded consciousness with disorientation, irrelevance in her talk and a tendency to perseveration. The fit which followed was typical with movements symmetrical on the two sides. For two to three hours afterwards there would frequently be intermittent clouding of consciousness with subsequent amnesia for the whole of this period. Her mood fluctuated between a euphoric elated state and bouts of depression with irritability and mild outbursts of temper. She was discharged on April 3, 1947, at her own and her family's wish. The only change in physical signs was appearance of some postural loss in left as well as right toes.

Her condition at home remained unchanged until June 4, when she again went into status epilepticus. Her doctor was called after some twelve hours of almost continuous unconsciousness. The patient came round on the following day, but developed signs of consolidation in the chest shortly afterwards and died on June 11 of broncho-pneumonia. In the five days preceding her death she was frequently disorientated and out of contact with her surroundings for two to three hours at a time, but had no further convulsive attacks. This case will be reviewed in the commentary on the families.

Case B.—Female, aged 61. Mother of patient A. She has never been ill and had not noticed any abnormality. On examination, however, there were the following positive findings: coarse tremor of upper limbs and slight titubating tremor of the head. Tremor not appreciably exacerbated on volition. Nystagmus to both sides, more marked to left. Exceedingly thin arms and legs, which had always been "like match-sticks" but no weakness in limbs or trunk. Ankle-jerks absent and left plantar extensor. B.P. 140/90. Early sclerotic changes in retinal vessels.

Personality was that of a stable, conscientious, hard-working woman, devoted to her seven children.

Case 12.—Brother of our propositus, aged 28, was examined and found to be normal.

The remaining five sibs of our propositus were unwilling to be examined, but were said to be healthy and without minor defects. The other cases shown in the pedigree were either inaccessible, unwilling to be examined or dead. Information about them was obtained from Case B, an observant and reliable witness.

Cases 1, 2, 3, 4, and 7, suffered from heart disease; Case 1 died suddenly of a "heart attack" at 62; Case 4 weighs 16 stones and has heart disease, which may be secondary to this; and Case 7 died at 34 of rheumatic heart disease. Obviously the diagnosis in the cases of sudden death may have been subject to considerable error. Nevertheless the history obtained was such a striking one that for reasons indicated below it is mentioned here.

Commentary on the Families

There were in our first family two cases of typical Charcot-Marie-Tooth disease (2, 8), one of them (2) also suffering from polycystic kidneys. One case (5) was diagnosed as an abortive Friedreich. This diagnosis is perhaps open to dispute, but there does not appear to us to be an alternative one for the combination of nystagmus, pes cavus, scoliosis, and absent deep reflexes. If discovered in a Friedreich family this case would certainly have been called an abortive Friedreich. Two cases (3, 7) were considered to be abortive forms of Charcot-Marie-Tooth disease. In the clinical picture and the benign character of the condition these two cases resembled the syndrome described by Roussy and Levy, although unlike the latter they had not had any disability in early childhood. There were three cases (10, 12, 14) of early abnormality in childhood which may develop into any of the conditions mentioned. Case 3 is suffering from a duodenal ulcer, as did Case 5, whose ulcer proved fatal. Another abnormality in the family which proved fatal was mitral stenosis in Case 6. In Cases 1, 2, and 5, there was gross emotional instability with violent aggressive outbursts and social irresponsibility due probably to constitutional psychopathy.

It will be noted that there was a marked variation in the age of onset of the disease in those members in regard to whom definite information was available. Such variation is rare in Friedreich's disease and peroneal atrophy, though it occurs in a small percentage of stocks. It may be that the trivial character of the disability in many of the cases renders the ages of onset subject to considerable error. However, this explanation does not hold for many of the other examples of this phenomenon, and for these there is a possible genetic explanation, to which we shall refer later.

Differential diagnosis and interpretation of Case A in our second family was difficult. Cerebellar neoplasm or tuberculoma were excluded by

normal C.S.F. findings, B.S.R. and X-rays, and a clinical picture that could be accounted for only by multiple or diffuse lesions. There was no spina bifida, skull and cervical spine X-rays were normal, and there was no other evidence for the presence of an Arnold-Chiari malformation. Absent reflexes and wasting excluded disseminated sclerosis. The combination of kyphoscoliosis, pallor of discs, nystagmus, cerebellar ataxia, pyramidal signs, absent reflexes, and symmetrical amyotrophy, was held to permit of no diagnosis other than Friedreich's disease. However, the marked wasting and its distribution in the lower limbs producing a typical "inverted champagne bottle" deformity, offered a further suggestion of some affinity between this condition and peroneal muscular atrophy. It will be remembered also that comparatively late onset and pallor of discs is commonly held to be more characteristic of the Marie type of hereditary ataxia.

Epilepsy is uncommon in Friedreich's disease, but several examples of the complication have been reported (Saquet, 1919; Wichtl, 1933; Bielschowsky, 1934). No pathological lesion has ever been found to account satisfactorily for the epilepsy. Friedreich's disease is rare and epilepsy common. The E.E.G., in our case, suggests that their combination here was probably fortuitous. The bilaterally synchronous paroxysmal high voltage delta activity and prominence of theta waves was consistent with the record of a young idiopathic epileptic. The patient's ataxia and dysarthria began when she was having relatively infrequent attacks. Nine months later there was a remarkably rapid deterioration after the first attack of status epilepticus. Epilepsy may give rise to ischæmic necrosis of nervous tissue as a result of anoxæmia during seizures (Meyer, 1939). In this case the degenerative process in previously vulnerable areas presumably underwent rapid acceleration, owing to anoxæmia induced by prolonged status epilepticus.

The signs in Case B suggested an abortive Friedreich, though her very thin legs were reminiscent of those of her daughter.

The high incidence of cardiac disease in this family is interesting in view of the frequent occurrence of congenital heart disease in Friedreich's ataxia (Rütimeyer, 1877; Aubertin, 1907; Mollaret, 1929).

In both the families the neurological disorders were handed down by a single parent, the gene responsible, as in the case of other families exhibiting a similar phenomenon (cf. Biemond, 1928; Gardner, 1906; Spillane, 1940), being an irregular dominant. The fact that different diseases, such as Friedreich's ataxia and personal muscular atrophy, can be produced separately or together in one patient by a single gene is a phenomenon of importance worthy of detailed consideration. An approach to the problem

can only be made in the present state of our knowledge through the genetics of these disorders.

The inheritance of peroneal muscular atrophy and Friedreich's disease.—In peroneal muscular atrophy three modes of inheritance have been described, dominant (Hänel, 1890), recessive (Steinthal, 1929) and sex-linked (Herringham, 1889; de Lisi, 1926). Bell (1935) showed that dominant inheritance was by far the commonest—recessive and sex-linked genes accounting for only a small proportion of pedigrees. In the case of retinitis pigmentosa, one of the five different genes which can produce it, a recessive, may be identified clinically by its causing deafness as well. In peroneal muscular atrophy the only difference described so far is that between the average age of onset of dominant and recessive forms, which are 18.95 and 10.93 years respectively (Bell and Carmichael, 1935).

In the early controversies on the genetics of Friedreich's disease, the discrepancies among the results of different authors were partly due to the fact that some treated the Friedreich and Marie forms separately (Dresel, 1917) while others (Mino, 1922; Hanhart, 1923) considered them to be variations of a single heredo-degenerative process. Bell and Carmichael (1939) surveyed 1,128 cases from the literature and studied 100 cases of their own. They concluded that recessive and dominant inheritance occurred in both Friedreich and Marie variants, although a large majority of pedigrees of the former and more than half of the pedigrees of the latter were recessive. They produced impressive evidence for the unity of the two diseases and familial spastic paraplegia. The sex distribution, average total duration and age at death were strikingly similar for each of the three diseases within both the recessive and dominant groups. Friedreich and spastic paraplegia also had a similar average age of onset in each group (11·75 years recessive and 20·42 years dominant and 11·36 years recessive and 18·60 dominant respectively) although the figures for spastic ataxia were significantly higher (14·72 years for recessive, 36·25 years for dominant). The consanguinity rate among parents of cases from recessive pedigrees was approximately the same for each of the three groups. The most convincing piece of evidence for the unity of the Friedreich and Marie syndromes was that in 35 out of 317 pedigrees both forms were present.

The investigations of Sjögren (1943) produced a rather different picture. He personally investigated a large series on which he reported in great detail. His results are not strictly comparable with those of Bell and Carmichael, as he used a more stringent classification. He divided his cases into five groups, of which Groups I and III roughly correspond to the Friedreich and Marie forms respectively. He concluded that these were genetically quite distinct, the former determined by a recessive, and the

latter by a dominant gene. However, any theory of the genetics of hereditary ataxia must take into account the many examples of families containing both diseases. That there are at least one dominant and one recessive gene, and that the average clinical picture resulting from the expression of each is different, cannot be disputed, but the existence of these mixed families strongly suggests that the clinical differences cannot be determined only by the main genes.

A phenomenon that has been observed in Huntington's chorea suggests a possible method of reconciling these conflicting findings. Pohlisch (1941) has pointed out that this disease shows a phenotypic variation with age. (Choreic symptoms are prominent in the mid-thirties, striate rigidity in the twenties, and intention tremor in the sixties.) Now, many of the families in which both Friedreich and Marie variants have been reported showed marked variations in the age at which the disease became manifest, the type of picture described by Marie occurring at the later age. Thus, in the family reported by Frey (1912), the grandfather suffered from the Marie type of disease, which commenced at 65, while his three grandchildren had Friedreich's disease, which commenced at or before 10 in each case.[1] Similar variations in age of onset were seen in the families described by Ormerod (1888) and Vorkastner (1914). There is a strong suggestion, therefore, that in hereditary ataxia too the clinical effect of a given gene depends upon the age at which it is expressed. Now, it is known that the age of onset tends to be very similar for members of the same family in a very large proportion of cases *(vide infra)*. The obvious deduction would appear to be that, in the small proportion of families in which the conditions have been found together, the age of onset has been pushed outside the usual limits for the main gene by external factors or the influence of the rest of the gene complex. This would explain why the conditions are largely distinct and also their occasional occurrence within the same family.

Bell and Carmichael's conclusion that Friedreich's ataxia, Marie's ataxia, and familial spastic paraplegia "were essentially conditions with a common source" was perhaps an over-simplification of the facts. As far as the Friedreich and Marie syndromes are concerned there are at least two genetic "sources," a recessive and dominant gene whose clinical effects are usually different and only exceptionally alike. Moreover,

[1] This pedigree on further examination proves to be highly signficant for the whole problem. Haldane has pointed out that, since the parents of the three grandchildren with Friedreich were double first cousins, the grandfather's condition was most probably due to the incomplete recessivity (in the heterozygous state) of the gene responsible for Friedreich. In other words, a smaller quantitative effect of the genetic process that produces Friedreich's disease may produce the Marie syndrome instead.

Haldane (1941) has recently shown that recessive spastic paraplegia was due to a partially sex-linked gene. This condition is therefore to a large extent distinct genetically from Friedreich and Marie.[1]

We have, therefore, a complex but highly interesting relationship between the three conditions. Genetically heterogeneous conditions such as recessive and dominant spastic paraplegia are clinically indistinguishable, while conditions as clinically diverse as the Friedreich and Marie syndromes and recessive spastic paraplegia may result from the expression of one and the same gene.

Rather more uncommon than families with both Friedreich and Marie forms of hereditary ataxia are those, such as our two families, in which features typical of Friedreich are associated with those of peroneal muscular atrophy, others in which hypertrophic interstitial neuritis occurs in addition (Biemond, 1928), and still others in which myopathy or Leber's hereditary optic atrophy are combined with Friedreich (*vide supra*). The genes responsible for such families would appear to be more highly pleiotropic than those producing the majority of cases of each of these diseases, and are therefore possibly distinct from them. In their expression it seems that the possible remote effects of the genetic processes producing Friedreich's disease, peroneal muscular atrophy, &c., are realized. The more remote the effects of a gene, the more infrequent and irregular are their expression. This may be the reason why families, in which different neurological syndromes or hybrid forms exist, are so rare. The overlap between the diseases combined in such families is small, but the fact that diseases such as hereditary ataxia and peroneal muscular atrophy can even rarely result from the expression of the same gene argues for some fundamental connexion between them. The genes responsible for complex pedigrees are nearly always dominant and more exposed therefore to selection, which favours modifiers that buffer their effects. Hence the variability in them of the clinical picture which may range from hybrid forms with serious disability to abortive forms with none (Family II), and perhaps also of the age of onset (Family I).

In a large majority of families of the Friedreich group and peroneal atrophy the age onset is remarkably uniform. Thus, in Bell's material the coefficient of correlation for age of onset between pairs of sibs was 0·925 for dominant Friedreich, and 0·840 for recessive peroneal atrophy. Haldane (1941) has pointed out that correlations of this order cannot be due to modifiers, except in individual cases where these may be closely linked with the main gene. He has suggested that there are three or four different main genes for each of the diseases showing a high

[1]To a large extent, and not completely, because Haldane showed that a partially sex-linked gene also accounted for a small proportion of Friedreich and Marie cases.

correlation coefficient and that each gene is responsible for an age onset within narrow limits. In the case of sex-linked spastic paraplegia the genes would have to be on the same chromosome and probably at the same locus, i.e. they would be allelomorphs at least three in number. Haldane therefore considers it probable that the genes for the other diseases with high correlation will prove to be multiple allelomorphs. Thus, not only are there dominant, recessive and sex-linked forms of hereditary ataxia and peroneal muscular atrophy, but evidence exists that each of these may be further differentiated into their separate allelomorphs.

Applying these facts to the three types of case mentioned above we would suggest that: (1) Mixed families such as those reported here are due to highly pleiotropic genes, probably distinct from those responsible for most cases of the separate diseases. (2) Abortive forms, when occurring in families together with the fully fledged diseases, are probably due to the action of genetic modifiers on the main gene. Where only abortive forms appear through several generations, however (Roussy and Levy, 1926; Symonds and Shaw, 1926), modifiers cannot be invoked in explanation, any more than in the case of uniformity in age onset. These families must represent the expression of separate genes, possibly one of the rarer allelomorphs of Friedreich's ataxia or peroneal muscular atrophy (cf. hæmophilia, where the rarer of the two allelomorphs produces a mild disease). (3) Abnormalities outside the C.N.S. (cf. polycystic kidney in our first and heart disease in our second family) have been too often recorded in families of Friedreich and peroneal muscular atrophy to be due to chance. They are probably indirect effects of highly pleiotropic genes.

Clinical and Genetic Methods of Classification

The facts we have discussed above are important for the difficult problems of classification and of the intermediate forms in the degenerative disorders. It will be apparent that terms such as "unity" or "affinity" when applied to groups of degenerative diseases, such as those we have been considering, are meaningless unless the terms of reference, whether genetic or clinical, are precisely stated, for the two are by no means equivalent. The definition of a clinical entity by means of more or less arbitrarily chosen clinical criteria may be useful in practice at a certain stage of knowledge of a group of diseases, but may obscure distinctions based on genetic factors. If one of the genes which can produce this entity should be rather more variable in its effects than the others, the status of some of the cases resulting from its expression may create a "problem" of classification. This is undoubtedly one way in which the difficulties arising from the existence of intermediate clinical forms, so common in the heredo-degenerative disorders of the nervous

system, are created. These difficulties may at present be unavoidable. The subtle distinctions which exist between the separate allelomorphs of hereditary ataxia or peroneal muscular atrophy (viz. the slight differences in average age of onset) and which may be found to distinguish cases of sex-linked Friedreich from those due to an autosomal gene, would be irrelevant in present-day clinical practice. A classification based on genetic type would, therefore, be of little value. At a later stage of our knowledge the distinction between the dominant, recessive, and sex-linked varieties of a degenerative disease may prove to be as important as that between the different types of streptococcus.

The Action of Natural Selection and its Possible Significance

The existence of separate genes and probably allelomorphs for both hereditary ataxia and peroneal muscular atrophy and other diseases is a phenomenon of exceptional interest, with important bearings on the problems of the heredo-familial degenerative disorders of the C.N.S. The dominant genes are more exposed to the action of natural selection, modifiers are accumulated which postpone their time of expression and attenuate their effects generally. The average age of onset of the disease produced by the dominant genes is also increased by the elimination of those genes expressed early in life. Since there tend to be at least subtle differences in the effects of the different genes, even if these are allelomorphs, this last process as well as the selection of modifiers causes some change in the clinical characteristics of the disease. There is evidence for such an effect by selection on the dominant genes for Friedreich's ataxia, spastic ataxia, &c. and peroneal muscular atrophy. The disease produced by the dominant genes appears at a significantly later age in each case (*vide supra*). Moreover, the age of onset, age at death, and duration, are all more variable in the dominant group. (Bell and Carmichael, 1935, 1939).

The postponement of age of onset by modifiers may have important secondary effects. The main gene is made to exert its effect at a later stage of development and in a different physiological environment. We would expect an alteration in the phenotype to result. In hereditary ataxia Haldane has shown that there were probably modifiers with considerable effect on age of onset in a small percentage of families.[1] If

[1]It would appear, therefore, that the Marie syndrome may result from one of three possible genetic processes: (1) from the expression of a dominant gene, possibly allelomorphic with that responsible for Friedreich; (2) through the action of modifiers postponing the age of onset of a gene which in the unmodified form produces Friedreich; (3) through the incomplete recessivity of the heterozyte in a Friedreich pedigree (cf. Frey's pedigree, *vide supra*). In pedigrees exhibiting the last two phenomena both the Friedreich and Marie variants could be expected to occur.

our explanation above for the occasional coexistence of the Friedreich and Marie forms in one family is correct, the selection of these modifiers has conditioned a relative increase in the numbers of cases of spastic ataxia.

These changes due to selection are comparatively small, but there is no reason why it should not have produced more fundamental alterations in disease entities. Thus Haldane (1942 I) has shown that a number of sex-linked modifiers affect the age of onset of Huntington's chorea. He suggests that in Sinanthropus it may have been a disease of infancy. If so, it must have been a very different sort of disorder, for it shows a well-marked phenotypic variation with age.

Now, comparisons have been frequently drawn between the heredo-familial degenerative disorders and the involutional changes in the C.N.S. occurring with senility. Such a comparison was the basis of Gowers' concept of abiotrophy for the degenerations of the C.N.S. It was recently revived by Spatz (1938) under the term of "Systemic atrophies." These concepts have recently acquired a new interest owing to the work of Meyer and Nevin (1947). In an important communication the Jakob-Creutzfeld syndrome they have drawn attention to the striking similarity between the neuronal degeneration of old age as described by Gellerstedt (1939) and Stern (1936) and those seen in the system degenerations. "Abiotrophy" was an interesting concept, but in the absence of any physio-pathology of senility it threw no light on the degenerative disorders of the C.N.S. Underlying all such concepts was the assumption that ageing was a physiological process and the disorders localized and precocious versions of it. However, "physiological" ageing and "natural" death are rather uncommon phenomena in nature. In the majority of species of mammals that have been studied, death (when not due to accident) and senescence have proved to be due to definite diseases. In the mouse, almost the only animal in which the pathology of old age has been systematically studied, a large fraction of deaths is due to cancer, which in mice is a genetically determined disease (Haldane, 1941, II). In other pure lines a cystic degeneration of the kidneys regularly develops in old age (Gorer, 1940).

We can obtain some suggestion as to the possible relationship between the heredo-familial degenerations and the changes of the C.N.S. in old age by pursuing a little further the line of thought commenced above. The postponement in the age of onset of a disease by modifiers is progressive. The modifiers are selected and spread through the species. The disease eventually begins after reproductive life and becomes one of old age. Selection is now unable to combat the reintroduction of the gene into the species by fresh mutation. The main gene causing the disease increases in frequency and unions of persons carrying it must eventually become

common (Fisher, 1931). There is, consequently, a tendency in a population for the accumulation in the post-reproductive period of an aggregation of genetically-determined pathological effects (which may have originally appeared in a different guise at an earlier age). In man, in spite of the obvious technical difficulties in the way of establishing the operation of genetic factors in senility, some evidence already exists to indicate their importance. Thus some senile conditions of the eye, such as pinguecula, pterygium, arcus senilis, and senile cataract (Vogt, Wagner, Richner, and Meyer, 1939) have been shown to have a genetic basis. Evidence also exists that arteriosclerosis is genetically determined (Mortensen, 1925).

To asume that the changes in the C.N.S. in old age are genetically determined and classifiable therefore with the heredo-familial degenerations is speculative, but not perhaps to the extent of explanations such as "wear and tear" often put forward to account for them. A genetic hypothesis gives us some insight into the similarities which have led to concepts such as "abiotrophy." It explains why the changes of senility in the C.N.S. are common, though neither inevitable nor invariable. It also accounts for the fact that the extent and effects of such changes are much less severe than those seen in the degenerations of earlier life. For, while at the time of their appearance as mutations the responsible genes may have had severe effects in early life, many of these will have been suppressed or slowed down in the course of their postponement to old age by the accumulation of modifiers. In old age, too, diseases may be cut short in the course of their evolution. It is possible therefore that the prospect has been opened up, by the concepts of modern genetics and neuropathology, of an attack on an important aspect of the problem of ageing via the degenerative disorders of the nervous system, and of a deeper insight into the latter by further investigation of the phenomenon of senility with a combination of clinico-pathological and genetic studies.

SUMMARY

(1) Two families providing further evidence for some connexion between Friedreich's disease and peroneal muscular atrophy are described.

(2) The genetics of these disorders are discussed. It is argued that the difficulties arising from the existence of intermediate forms are consequent upon the system of classification by physical signs which may cut across the boundaries set by genetic factors.

(3) The genetic relationship of the various transitional and abortive forms to the main clinical syndromes is discussed.

(4) The importance of the phenomenon of several genes producing the same disease is stressed. The action of natural selection in separating

clinically the different genetic groups within a disease entity is described. The possible significance of this for the problem of the resemblance between the heredo-degenerative disorders of the nervous system and the C.N.S. changes in old age is considered.

I am indebted to Dr. Eliot Slater for encouragement, criticism and suggestions. I also want to thank Dr. W. Russell Brain and Professor Aubrey Lewis who read the paper and offered helpful criticism.

REFERENCES

AUBERTIN, C. (1904) *Arch. Gen. Med.*, **194**, 1993.
BALLET, C., and ROSE, F. (1905) *Nouv. Icon. de la Salpêtrière*, **18**, 404.
BAUER, and GY (1909) *Rev. Neurol.*, **17**, 97.
BELL, J., and CARMICHAEL, E. A. (1935) On the Peroneal Type of Progressive Muscular Atrophy. *The Treasury of Human Inheritance*, **4**, 69.
——, —— (1939) On Hereditary Ataxia and Spastic Paraplegia, *The Treasury of Human Inheritance*, **4**, 141.
BIELSCHOWSKY, M. (1934) *Z. ges. Neurol. u. Psychiat.*, **150**, 373.
BING, R. (1905) *Dtsch. Arch. f. Klin. Med.*, **83**, 199.
BIEMOND, A. (1928) *Dtsche. Z. f. Nervenh.*, **104**, 113.
BOGAERT, L. VAN, and BORREMANS, P. (1932) *Rev. Neurol.*, **1**, 165.
CURTIUS, F. S., STÖRRING, F. K., and SCHÖNBERG, K. (1935) *Z. ges. Neurol. u. Psychiat.*, **153**, 719.
DE LISI, L. (1926) *Riv. di Pat. Nerv.*, **31**, 390.
DRESEL, K. (1917) *Virchow's Arch.*, **224**, 256.
FERGUSON, F. R., and CRITCHLEY, MACDONALD (1928) *J. Neurol and Psychopath.*, **9**, 120.
FISHER, R. A. (1931) "The Evolution of Dominance," *Biol. Rev.*, **6**, 345.
FREY, K. (1912) *Dtsch. Z. f. Nervenh.*, **44**, 351.
GALLIOTTI, O. (1928) *Rev. Neurol.*, **2**, 758.
GARDNER, E. (1906) *Brain*, **29**, 112.
GELLERSTEDT, N. (1933) Zur Kenntnis der Hirnveränderungen bei der Normalen Altersinvolution, *Upsala läkaref. förh.*, **38**, 193.
GHILARDUCCI, F. (1906) *Policlinico*, **13**, 1442.
GORER, P. A. (1940) *J. Path. Bact.*, **50**, 25.
HÄNEL, H. (1890) Pedigree in *Treasury of Human Inheritance*, 1935, **4**, 69.
HALDANE, J. B. S. (1941) I, *J. Genetics*, **41**, 141.
—— (1941) II, *J. Genetics*, **41**, 149.
—— (1941) III. New Paths in Genetics. Allen & Unwin Ltd., London.
HANHART, E. (1923) *Schweiz. Arch. f. Neurol. u. Psychiat.*, **13**, 297.
—— (1923) *Schweiz. Med. Wchnschr.*, **1**, 129.
HERRINGHAM, W. (1889) *Brain*, **2**, 230.
JASTROWITZ, H. (1911) *Neurol. Centralb.*, **30**, 426.
KLEIN, D. (1937) *Schweiz. Arch. f. Neurol. u. Psychiat.*, **39**, 89 - 116, 320 - 329.
MEYER, A. (1939) *J. Ment. Sc.*, **85**, 927.
——, and NEVIN, S. (1947) Unpublished Communication.
MINO, P. (1922) *Policlinico*, **29**, 615.
MOLLARET, P. (1929) La Maladie de Friedreich, Masson, Paris.
ORMEROD, J. A. (1888) *Brain*, **10**, 461.
PERRERA, E. (1906) *Arch. di Psichiatr.*, **27**—Quoted by Kinnier Wilson in "Neurology," London, 1940, 956.
PINES, I.-L. Ja, and TRON, F. (1925) *Z. ges. Neurol. u. Psychiat.*, **95**, 762.

POHLISCH, K. (1941) Proc. 7th Internal. Genet. Congr. 1939, Cambridge 1941, 239.
POPOW, A. (1932) *Rev. Neurol.*, **2**, 447.
RAYMOND, F. (1905) *Nouv. Icon. de la Salpêtrière*, **18**, 5, 121.
——, and ROSE, F. (1909) *Encéphale*, **1**, 209.
ROMBOLD, C. R., and RILEY, H. A. (1926) *Arch. Neurol. and Psychiat., Chicago*, **16**, 301.
ROUSSY, G., and LEVY, G. (1926) *Rev. Neurol.*, **33**, 427.
RÜTIMEYER, L. (1887) *Virchow's Arch.*, **91**, 106.
SAQUET, R. (1919) *Thése de Paris.*
SJÖGREN, T. (1943) *Acta Psychiat. et. Neurol., Suppl.*, 27.
SÖDERBERGH, G. (1910) *Rev. Neurol.*, **20**, 7.
SPATZ, H. (1938) *Arch. f. Psychiat.*, **108**, 1.
SPILLANE, J. D. (1940) *Brain*, **49**, 397.
SPILLER, W. G. (1910) *J. Nerv. and Ment. Dis.*, **37**, 411.
STEINTHAL, M. (1929) *Arch. Rass v. Gesell. Biol.*, **21**, 425.
STERN, K. (1936) *Z. ges. Neurol. u. Psychiat.*, **155**, 543.
SYMONDS, C. P., and SHAW, M. E. (1926) *Brain*, **49**, 397.
VOGT, H., WAGNER, H., RICHNER, H., and MEYER, G. (1939) *Arch. Julius Klaus-Stiftung*, **14**, 475.
VORKASTNER (1914) *Med. Klin.*, **10**, 360.
WERTHEMANN, A. (1927) *Z. ges. Neurol. u. Psychiat.*, **111**, 683.
WICHTL, O. (1933) *Arb. a. d. Neurol. Inst. Wien*, **35**, 132.
WUTSCHER, L. (1910) *Med. Klin.*, **6**, 1932.

THE LIPIDOSES AND THE CENTRAL NERVOUS SYSTEM

BY

ALAN BIRD

(From the Department of Pathology, The National Hospital, Queen Square, London)

THE lipidoses[1] constitute a group of diseases in which the cellular metabolism of various lipid substances is abnormal. The disease may be confined to the reticular and histiocytic cells, notably in the spleen and liver, or may affect the ganglion cells of the central nervous system, with or without involvement of the reticulo-endothelial system.

Much has been done to elucidate the problem of these diseases of the nervous system since Waren Tay (1881) drew attention to the retinal changes of the condition, later designated *amaurotic family idiocy*. Sachs (1887) first described the fundamental and essential nerve cell changes underlying not only this, but other related states. In the period which followed, various clinical subgroups were reported which differed in respect of their age of onset and clinical features. These conditions came to be regarded as disease entities with the discovery that the subgroups showed certain differences in their staining reactions, and that in one group one portion of the brain, e.g. the cerebellum or retina, was involved to a greater extent than in the others.

There may be some justification for recognizing the clinical subgroups because they present certain distinctive features, according to their age of onset, which tend to run true to type.

AMAUROTIC FAMILY IDIOCY

Congenital form.—A congenital form has been described by Norman and Wood (1941) in which death occurred soon after birth. Post-mortem examination revealed arrested cerebral development with widespread involvement of the nerve cells in both the cerebrum and cerebellum.

Infantile form.—The infantile form presents characteristically the appearance described as the "cherry-red spot" in the fundi. The infant

[1] The term "lipid" is the one recommended by the International Congress for Pure and Applied Chemistry. The name recommends itself for the following reasons: (a) its derivation is suitable, (b) it is general enough to include the diverse members of the group, and (c) it has not been used for any of the subgroups. Lipids may be defined as a group of naturally occurring substances consisting of the higher fatty acids, the naturally occurring compounds, and substances found naturally in chemical association with them.—Bloor, W. R. "The Biochemistry of the Fatty Acids and Their Compounds, the Lipids." Am. Chem. Soc. Monograph Series, No. 33, New York.

progresses normally up to the age of 6 or 8 months and then it starts to retrogress. Mental deterioration is associated with the development of progressive muscular weakness and amaurosis. In the later stages the extremities become spastic, the only movements being muscular twitching and myoclonic spasms precipitated by external stimuli such as touching or even a loud noise. Death usually occurs within a year from the time of onset from marasmus aggravated by an inability to swallow. Infantile amaurotic family idiocy has a marked predilection for Jews and affects females three times as frequently as males, features not shared by the other groups.

Late infantile form.—A "late infantile form" is described resembling the foregoing but commencing at the age of 3 or 4 years. It tends to run a more chronic course and optic atrophy is a feature, the cherry-red spot being the exception rather than the rule. No racial predilection has been observed (Batten, 1903).

Juvenile form.—The juvenile form generally has its onset between the sixth and twelfth years. There is a slowly progressive deterioration of intellect along with the development of blindness and spastic paralysis. No cherry-red spot is seen but retinitis pigmentosa often occurs. It may be present also as the only sign of abnormality in the parent of a child developing amaurotic idiocy. The cerebellum tends to be affected more than in the other subgroups. Greenfield and Holmes (1925) have shown that in the retina of the juvenile form it is chiefly the outer granular layer of cells which is destroyed, whereas the ganglion cells degenerate in the infantile form (Grinker, 1927).

Adult form.—An adult form has come to be recognized with its onset usually in the third decade or even later. The picture is that of a slow mental involution, not unlike general paralysis, associated with the development over the period of many years, of extrapyramidal rigidity, incoordination and bulbar signs. Retinitis pigmentosa may be present or optic atrophy leading on to blindness, but visual disturbance is exceptional (Van Bogaert, 1937). Kufs (1928) described a case of insanity developing at the age of 29 years with progressive mental deterioration but no visual loss or eye changes. Autopsy performed nine years later revealed changes exactly resembling those of amaurotic idiocy.

Niemann-Pick Disease

The Niemann-Pick disease entity is an affection mainly of Jewish female infants in which the lipid dystrophy affects the reticulo-endothelial cells causing enlargement of the liver, spleen and, to a lesser extent, lymph glands. There may be brownish pigmentation of the skin, ascites, œdema of the hands and face, slight anæmia and leukopenia. The condition was

long believed to be a disease entity. Knox, Wahl and Schmeisser (1916) described a case, however, combining the features of Niemann-Pick disease and the changes in the central nervous system of amaurotic idiocy. They regarded this as a curious co-ordination of two distinct diseases. Ludo van Bogaert (1937) drew attention to the close relationship between the two affections when he described a family in which one child has Niemann-Pick disease and another, so-called "pure" amaurotic idiocy. Furthermore, Bielschowsky (1928) in two cases diagnosed as classical examples of amaurotic idiocy was able to demonstrate the presence of lipid-distended cells in the liver and spleen, identical with those present in Niemann-Pick disease. The first was in an infant of Dutch parents and the second, a case recorded by himself and Pick (1927). Similar findings have been reported by Davidson and Jacobson (1936). Thus, the very close relationship between the two conditions has been clearly established clinically. Histological examination has confirmed this belief and has shown that from a neurological point of view, the pathological changes are identical.

Gaucher's Disease

The spleno-hepatomegaly of Niemann-Pick disease brings this condition into line with Gaucher's disease, also an abnormality of lipid metabolism. The lipid accumulates chiefly in the spleen, liver, bone-marrow and lymph glands. The reticulum cells distended with lipid have a characteristic appearance diagnostic of the condition. The skin may show a copper-coloured pigmentation. Pingueculæ, uniform, brownish plaques on the conjunctivæ, on either side of the cornea, are said to be pathognomonic. Thrombocytopenia may lead to a hæmorrhagic tendency and secondary anæmia. For long it was believed that the changes were confined to the reticular cells of the lymph-hæmopoietic organs. In 1921, however, Rusca described an infantile form of Gaucher's disease involving the central nervous system. In 1927 Oberling and Woringer threw further light on the problem by reporting a family of four siblings all of whom died within the first year of life of Gaucher's disease with central nervous system involvement. Giampalmo (1946) in reviewing the literature up to 1946 comments on 25 cases of Gaucher's disease involving the central nervous system. In this series 23 died before reaching the age of 18 months, one at 19 months, and the other at 2 years. The clinical picture of those developing neurological symptoms is fairly characteristic. An infant with hepato-splenomegaly of early onset, perhaps with pigmented skin and pingueculæ, retrogresses mentally into a state of apathy and somnolence with catatonia. Marked muscular hypertonia produces increased reflexes, and opisthotonus with neck rigidity. Diagnostic signs are internal strabismus, at first transient and later permanent, trismus, dysphagia and

attacks of laryngeal spasm producing cyanosis. The marked cachexia resulting from the dysphagia usually causes death within a year. The diagnosis is established for certain by demonstrating Gaucher cells in biopsy material from the sternum or spleen. Very rarely foam cells are seen in a blood smear.

Many believe that the central nervous system is involved only in the infantile form of Gaucher's disease, but there are rare cases suggesting that even adults may have neurological involvement. van Bogaert and Fröhlich (1939) described a case of Gaucher's disease affecting a Polish-Jewish male of 42 years who had hypertonia of extrapyramidal type, increased reflexes in the lower limbs, and painful cramps in hyperextension. No histological examination was made. Davidson (1942) called attention to a 26-year-old Polish-Jewish male with Gaucher's disease causing skin pigmentation, pingueculæ, enlarged lymph glands, hepatosplenomegaly, and bony involvement resulting in dorsal kyphosis. He had a set expressionless face suggestive of a lesion in the basal ganglia. Histological examination of the central nervous system revealed that "many of the large cells of the putamen and caudate nuclei disclosed loss of Nissl substance, swelling of their bodies and displacement of the nucleus to the periphery. Some of the nerve cells were completely disintegrated. The Purkinje cells, although slightly swollen, appeared normal. Large foam cells containing irregularly shaped nuclei usually placed at the periphery and containing pale staining cytoplasm were seen in the spinal cord. Similar changes were found both in the anterior and posterior roots." Davidson did not attribute these changes to Gaucher's disease, but their similarity to the case to be described will be apparent.

Hand-Schüller-Christian disease and essential xanthomatosis, both lipidoses, have not been discussed as in neither is there clear evidence that nerve cells become infiltrated with lipid. The former condition may produce neurological symptoms by pressure effects from dural plaques, or more rarely, by irregular patches of demyelination scattered in the white matter.

Although the above subdivisions may be of some clinical value, they are by no means clear-cut, and much overlapping occurs. Infantile cases of amaurotic idiocy have been described without the cherry-red spot, while a typical juvenile case developed the cherry-red spot at the age of ten years (Wyburn Mason, 1943). Bertrand and van Bogaert (1934) reported a family, the first two children in which developed typical infantile amaurotic idiocy, while the third became demented at the age of 3 years and at 18 years showed no retinal changes. Greenfield and Nevin (1933) described two siblings, one of which developed typical infantile amaurotic idiocy, the other the juvenile form, thus calling attention to the very close relation-

ship between the two groups. In 1918 Walter described three members of a family with idiocy and nervous lesions, but no amaurosis or retinal changes. One of them died, aged 23 years, and histological examination revealed that the nerve cells were infiltrated with lipid as in a typical case of amaurotic idiocy. Kufs' case of an adult with dementia commencing late, not associated with blindness, but resembling typical amaurotic idiocy at autopsy has been referred to above.

Many more examples of these anomalous cases could be quoted to show first, that any clinical classification must, at best, be tentative, and second, that signs and symptoms formerly regarded as pathognomonic of one group are known to appear sporadically in an apparently distinct group, thus pointing to some underlying factor common to all forms. This factor is the infiltration of nerve cells with lipid; it is present in every type as is borne out by the literature and the cases now to be described.

Report of a Case of Gaucher's Disease with Involvement of the Central Nervous System

The first case is of special interest; it is that of a child of school age who developed Gaucher's disease with severe involvement of the nervous system. As has been pointed out above the literature contains numerous reports of this syndrome affecting infants but no reference has been found to any proved case in an older child in which the nervous tissue was affected. The diagnosis was substantiated during life by histological examination of the spleen following splenectomy. Post-mortem examination confirmed this beyond doubt, by staining reactions and biochemical investigations.

Case 1.—V. C., a boy of 11 years, was admitted in 1942 to Chase Farm Hospital under Dr. Russell Brain. The parents were healthy, non-Jewish and not consanguineous, nor was there any serological evidence of syphilis in either. The mother had contracted no illness prior to his birth, but had a history of two earlier miscarriages, both at about the third month. His birth had been easy, unassisted by instruments. The only other child of the family, a boy aged 5 years, was apparently normal.

Up to his seventh year the patient progressed normally and was able to attend an ordinary school until this age. At this stage a gradual mental deterioration commenced and by the following year he had retrogressed to such an extent that he had to be sent to a special school, as he was restless and difficult to control.

During the last year of his life some four years after the onset, his condition went downhill more rapidly. He was incontinent of urine and unable to converse and did not recognize his mother. *Petit mal* attacks commenced about this time.

On examination he was found to be facile, with frequent inane grins and occasional peals of abnormal laughter. He had a pink and white complexion with no evidence of pigmentation. The cervical lymph glands were palpable and the spleen was enlarged three fingers below the costal margin, being firm and insensitive. The liver was not enlarged. His vision seemed unaltered and the fundi were normal. The pupils reacted sluggishly to light. The limbs showed hypertonus with exag-

gerated reflexes and "lead-pipe" rigidity but the plantars were normal. There were no other abnormalities of the sensory system.

Splenectomy was performed by Mr. R. Galloway, the spleen weighting 558 grammes (19·5 ounces). His condition did not improve, however, and he died some six months later.

Investigations carried out during life.—Plasma cholesterol, 230 mg. per 100 c.c. Plasma fatty acids, 320 mg. per 100 c.c. Plasma lecithin, not raised. Plasma total lipids, 2,500 mg. per 100 c.c.

Cerebrospinal fluid: Cells 3, total protein 30, W.R. negative.

Blood Wassermann reaction negative.

Hæmogram: R.B.C. 5,500,000, Hb. 92 per cent, W.B.C. within normal limits.

Autopsy.—The brain, which weighed 1,150 grammes, appeared normal macroscopically.

Histological examination.—Nerve cells throughout the brain and spinal cord, with few exceptions, were diffusely affected. The motor area and frontal cortex were more involved than the temporal and occipital cortex, but even here, numerous cells showed lipid swelling.

Cerebral cortex.—In the motor cortex the cyto-architectonics were grossly abnormal, party owing to a disappearance of many of the pyramidal cells, partly due to the deformity of the remaining cells and partly to the glial reaction. The pyramidal cells no longer retained their laminated arrangement and neither of the granular cortical layers was well defined. All of the ganglion cells were affected, particularly the larger ones of the deeper part of the third and the fifth cortical layers. They were swollen and rounded in outline, some being pyriform and others showing ballooning of one part of the cytoplasm. The nuclei retained their shape well but lay eccentrically, displaced either to the periphery or to the axonal base. The cytoplasm appeared finely granular, generally with loss of Nissl substance. The Nissl bodies, retained in a few cells, were peripherally placed. Many of the nerve cells were undergoing degeneration: examples of neuronophagy and satellitosis were to be seen and numerous glial stars. There were many compound granular corpuscles which tended to be accumulated in peri-vascular spaces. Frozen sections stained by Da Fano's modification of Bielschowsky's method showed that within the cell the neurofibrils were displaced to the periphery and that a few of the dendrites had globular swellings, some immediately adjacent to the nerve cell, others further along the course of the dendrite. Isolated dendrites showed "stag-horn" broadening reminiscent of the condition described as occurring in the cerebellum typically in the juvenile form of amaurotic idiocy. The white matter was apparently normal.

The frontal cortex showed similar severe changes but in the temporal lobe the cyto-architectonics were less upset. Both the second and the fourth layers were fairly well demarcated, and a much smaller percentage of nerve cells was affected. The hippocampus was well preserved. The occipital cortex was even less involved, many of the nerve cells being normal.

Basal ganglia.—A section at the level of the basal ganglia revealed that the large nerve cells of the caudate nucleus, putamen and globus pallidus were greatly swollen. The changes were similar to those observed elsewhere. In the putamen globular axonal swellings were noted in one or two places. In the thalamus the involvement of nerve cells was extremely widespread. The pulvinar showed similar abnormalities as did also the superior colliculus. In the paraventricular nucleus of the hypothalamus, certain of the nerve cells showed vacuolation, while others appeared as ghosts with faintly staining or absent nuclei. A few of the larger cells showed clearly outlined ballooning. The majority of the cells in the subthalamic nucleus and the smaller cells of the claustrum seemed normal.

Mid-brain.—In the mid-brain, the cells of the red nucleus, substantia nigra and

corpus mammillaria were severely involved and showed typical swellings. The oculomotor nuclei were well preserved and the nerve cells of the tuber cinereum were little affected.

Medulla.—At the level of the medulla a few of the cells of the nucleus ambiguus and XII nerve nucleus showed slight swelling, but the cells of the V and VIII nerve nucleus were apparently unaffected.

Spinal cord.—Sections of the cord from the cervical (C.7), thoracic (T.1) and lumbar (L.2) areas showed that the cells of the anterior horns showed marked ballooning, the cytoplasm containing a finely granular substance. Some of the less affected cells showed Nissl bodies but these were peripherally distributed. Others showed chromatolytic changes while yet others were undergoing disintegration with evidence of satellitosis and glial stars. In the posterior horns, the changes were less obvious: vague, oval-shaped, unstained bodies, faintly granular with no nucleus or Nissl bodies were seen.

Cerebellum.—The most prominent change in the cerebellum was a general shrinkage of the granular layer with the Bergmann cell layer standing out prominently. The Purkinje cells were fewer than normal but no swellings of the cell bodies were noted, though in the molecular layer, some "stag-horn" swellings of the dendrites were to be seen. The dentate nucleus appeared unaffected. Da Fano preparations revealed that the pericellular "basket" fibres around many of the Purkinje cells were deficient and there were isolated examples of argentophilic axonal swelling, sometimes referred to as "axonal torpedoes." With phosphotungstic acid-hæmatoxylin staining no increase of glial tissue was noted in the molecular layer but there was a proliferation in the neighbourhood of the dentate nucleus.

Staining reactions.—With Scharlach and hæmalum stain the great majority of intracellular granular swellings remained unstained in all areas. In a few of the cells of the nucleus ambiguus the lipid stained a faint salmon-pink colour, and in the spinal cord also, some of the nerve cell swellings took up some stain, their colour varying from pale pink to orange, even to a purplish tint. In isolated areas in the cerebral cortex, in the caudate nucleus and putamen, and in the Virchow-Robin spaces of the white matter, compound granular corpuscles were noted, stained a bright red colour.

Frozen sections stained by a modified Weigert method (Hurst, 1925) mordanted for from one to six days failed to stain the intracellular granules. Kultschitzsky's method also failed to stain the substance. The method suggested by Franco and Wolman (1947) which includes boiling at a pH 4·0 and the use of Sudan III was no more successful.

These staining reactions are in accord with descriptions of those of the lipid in the spleen in Gaucher's disease (Rowland, 1931; Epstein, 1924) and in the nerve cells of infantile Gaucher's disease (Lindau, 1930; Bloom, 1925; Kohne, 1938).

Spleen.—The reticular cells of the pulp were diffusely hypertrophied. Large cells, some of them multinucleated with finely granular cytoplasm, were grouped together. Like the intracellular contents of the ganglion cells the lipid did not stain with Sudan III, Scharlach or by the Smith-Dietrich method. Even boiling did not alter the staining reactions. These appeared to be typical Gaucher foamy cells. In places some of these cells had broken down and the lipid was phagocytosed by histiocytes.

Suprarenal.—The cells of the cortex were diffusely swollen, their cytoplasm being finely granular. In the medulla there were isolated globular shaped cells with the same granular, translucent appearance as those in the cortex. They showed the same staining reactions as those described above.

Lymph glands.—Isolated "foamy" cells were to be seen within the follicles.

Liver.—In the liver there were circumscribed nodules in which the cellular archi-

tecture was lost. These showed endothelial cells distended with lipid, an increase in fibro-blasts, round-cell infiltration and occasional multinucleated cells.

No "foamy" cells were found in the heart muscle, lungs or kidneys.

Biochemical investigations.—The value of the chemical analyses of the brain and spleen was reduced by the fact that they were carried out after the organs had been fixed in formalin over a period of years. Nevertheless, even after this time the amount of cerebroside was found to be considerably raised.

	Total phospholipid as phosphorus (grammes %)	*Saponifiable phospholipid as phosphorus (grammes %)*	*Spingomyelin as phosphorus (grammes %)*	*Cerebroside, actual weight not purified*
Brain	0·660	6·410	0·250	—
Spleen	0·246	0·216	0·030	0·97% of dry weight

These analyses were carried out by Dr. M. A. Bundock working in the Clinical-Pathological Laboratory of the National Hospital.

The chief interest of this case lay first, in the age of the patient, most cases of Gaucher's disease with nervous system involvement reported in the literature having been infants, and second, in the striking similarity in the histopathological changes between it and the cases of amaurotic family idiocy which are now to be described.

Case 2.—A. H., a female aged 4 years, was the only child of non-Jewish, healthy parents. Her mother's aunt developed fits at childbirth and her mother's cousin had fits for a time in her teens.

She developed normally up to the age of 2 years and 9 months, reaching the usual landmarks of childhood satisfactorily, learning to speak and even to repeat nursery rhymes. At this age she had her first seizure. During the following fifteen months up to the time of her admission, she had frequent seizures, usually at night. On some occasions she would blink her eyes and say that she was going to fall, without actually doing so. At other times she would fall and lie jerking without losing consciousness.

By the age of 3½ years her seizures were very frequent and she had developed weakness and unsteadiness of the right arm and leg, and her speech had deteriorated markedly, so that she was unable to form the simplest of sentences. Examination at that time revealed that her arms were very clumsy with very little independent finger movements. She was having frequent minor seizures and some major ones. She was treated with luminal and epanutin with a temporary improvement, but then, according to her mother, became much worse.

She was admitted to hospital and was observed to be having continuous myoclonic movements all over her body; the eyes jerked upwards, the tongue jerked almost regularly, and the lips made sucking movements. Her arms were sometimes flung widely into the air, or her legs brought up suddenly into acute flexion. The myoclonic movements continued at intervals of 3 to 8 seconds, even in her sleep. She was very weak, being unable to walk and sagging loosely to the side when held up.

Her cerebrospinal fluid at this time contained 2 lymphocytes per c.mm. and a total protein of 15 mg.; its Wassermann reaction was negative.

She was treated on tridione 0·3 gramme three times daily with marked improvement, the myoclonic jerkings coming to an end. She was able to sit up unsupported, and was beginning to take an interest in her surroundings when she was discharged from hospital.

The improvement was short lived, however, and one month later she was again having major attacks with almost continuous myoclonic movements. She then had a series of frequent major attacks which left her hemiplegic on the left side.

She was very weak, almost entirely lacking in voluntary movements. The myoclonic jerkings remained.

She was admitted to the National Hospital under Dr. M. J. F. McArdle, and was found to be stuporous, taking no interest in her surroundings. She was almost unable to swallow and appeared to have little power in her limbs. Her arms had almost continuous myoclonic movements of small amplitude and were held flexed. Her legs were less affected and in extension. All the deep reflexes were exaggerated, the abdominals absent, and the plantars extensor.

Four months before her death, her vision was observed to be failing. This continued until she seemed completely blind. One month prior to death the optic discs were pale and flat, but no cherry-red spot was noted.

An X-ray examination showed that her ventricular system was normal, but a little pooling of air on the convexity was suggestive of cortical atrophy.

She died nineteen months after the onset of her illness.

Autopsy (this examination was carried out by Dr. J. G. Greenfield).—The skull was abnormally thick for the age of the patient with no convolutional markings towards the vault. The dura was thick and lax, and the cisterna magna very large from cerebellar atrophy. The cerebellar folia were firm to the touch and stood out as ridges. The subarachnoid space was deeper than normal and the arachnoid appeared opaque. The liver (520 grammes) and spleen (47 grammes) were not enlarged. Both eyes were removed after previous injection of 25 per cent formalin. The macula was a dark red spot surrounded by a zone of pigmentation.

Histological examination.—Cerebral cortex—All parts of the cerebral cortex were affected but the postparietal region showed the most extensive degeneration, even amounting to actual softening in places. There was a tendency here for the grey matter to become decorticated, the line of cleavage running between the third and fourth cortical layers. The nerve cells were distended with fine granules of lipid which stained an orange-yellow colour with Scharlach R. and hæmalum, not the bright rose-pink usually found in infantile forms. From the staining reactions, the lipid seemed exactly similar to that described by Greenfield and Holmes (1925).

Occipital cortex.—In the occipital cortex there was a general reduction in the number of nerve cells present. The outer granular layer had almost disappeared while the fourth layer was barely discernible. The normal cellular arrangement was lost and the pyramidal cells seemed to have a random distribution. They were blown up with lipid which appeared in the cytoplasm as fine, bright orange granules with Scharlach staining. The intracellular lipid was not doubly refractile. Many cells were undergoing degeneration and there were many examples of neuronophagy. Glial reaction was marked, especially of fibrous astrocytes and oligodendroglia.

All cortical areas examined showed similar changes though not quite as severe as those in the post-parietal region.

Basal ganglia.—In the basal ganglia there was widespread involvement of nerve cells but the large cells of the globus pallidus and putamen were most distorted by the intra-cellular lipid accumulations. Many of the cells were disintegrating and were surrounded by compound granular corpuscles whose contents stained bright red with Scharlach and showed birefringence. These "gitter" cells accumulated in clumps in perivascular spaces in the white matter.

In the thalamus, many nerve cells had broken down and much of the lipid, apparently unaltered (orange coloured with Scharlach and not doubly refractile), was lying between the remaining cells.

Brain-stem and spinal cord.—Nerve cells throughout were distended with lipid and showed similar changes to those described above. Kultschitzsky's method revealed that the fibre tracts throughout were normal.

Cerebellum.—The cerebellum as a whole was atrophied with a reduction in the number of folia present. The molecular layer was extremely narrow and the

granular cell layer was almost totally deficient in neurons. There was a conspicuous reduction in the number of Purkinje cells and in some folia they were entirely absent. Many of the remaining ones were swollen with lipid, and their dendrites showed "stag-horn" swellings. Others appeared to have burst, the lipid dispersing into the intercellular spaces and being taken up by compound granular corpuscles.

Bielschowsky silver impregnations demonstrated the changes in the Pudkinje cells very well, both in the cell bodies and in the dendrites. Pericellular "basket" fibres had disappeared completely. There were a few argentophilic globular swellings both on the dendrites and the axons, the so-called degenerative "torpedoes." No other abnormality apart from these swellings was seen in the white matter; no areas of frank demyelination were observed, although colour changes with Scharlach were suggestive of very early degeneration in one or two places.

Glial reaction was marked throughout the cerebellum. Holzer preparations stained well the dense accumulation of glial fibres in the narrowed molecular layer.

Retina.—A percentage of the ganglion cells were distended and considerably larger and paler than those unaffected. Although specific fat stains were not used, the appearance of these cells so closely resembled those elsewhere in the nervous system, that it seemed a reasonable assumption that the substance was a lipid. Some of the ganglion cells were disintegrating and had evoked a response on the part of compound granular corpuscles. A few of these cells, bloated with lipid, lay in the neighbourhood of capillaries.

The most marked change was confined to an area within 3 mm. of the macula and consisted of a disappearance of the outer nuclear layer with an increase in glia at the site of degeneration.

The layer of pigment epithelium was irregular and showed patchy areas of degeneration. Some of the pigment had migrated and lay within the sclerotic tissue which was replacing the degenerated outer granular layer. The choroid was normal.

These changes resemble those described by Greenfield and Holmes (1925), but were limited in this case to the area immediately surrounding the macula.

Solubility of the lipid.—Tests carried out in accordance with the methods suggested by Weston Hurst (1925) showed that the lipid was soluble only in chloroform, a finding in keeping with his own and compatible with the concept that it was one of the sphingomyelins. Other solvents used were acid alcohol, ether, alcohol (95 per cent).

The liver, spleen, thyroid and suprarenals were examined and found to be normal.

Case 3.—P. L., aged 9 years, was the son of healthy, non-Jewish parents who were, however, cousins. He was the third child of a family of four, the first having been stillborn, the second, age 13½ years, healthy both physically and mentally, and the youngest, a boy age 20 months, so far normal. The patient's birth weight was 9¼ lb., the labour being difficult and lasting forty-eight hours. No birth injuries were noted.

He developed normally up until the age of 5 years when his school teacher complained that he was no longer making progress and that he tended to roam about the classroom. By the following year he was very backward mentally, and losing the power of his legs. He was noticed by his mother to grope for things that he had dropped on to the floor.

At the age of 7 years he could hardly walk at all and his vision was limited to the recognition of light only. He was found to have bilateral optic atrophy with slight papillœdema and very sluggish pupils; there was no cherry-red spot. X-ray examination of the skull showed no abnormality and the cerebrospinal fluid was normal. At this age, too, he started having generalized epileptic fits which became more frequent as he grew older. He developed incontinence of urine and fæces.

On examination he was found to be extremely weak, with constantly altering

bizarre attitudes, and his movements were ataxic. He screamed from time to time and uttered inarticulate noises. The reflexes were brisk and the plantars extensor. He resented being examined and no satisfactory sensory tests could be carried out.

His condition continued to deteriorate until his death at the age of 9 years.

Autopsy (this examination was carried out by Dr. J. G. Greenfield).—The liver and spleen were not enlarged. No lipid-distended cells were found anywhere in the reticular-endothelial system. The thymus was hypertrophied, but other endocrine glands appeared normal. The cerebellum was firm and atrophic but the rest of the brain showed no abnormality macroscopically.

Histological examination.—Cerebral cortex—Lipid infiltration of nerve cells with degeneration and a reduction in their total number, and glial reaction, similar to the changes described in Case 2 were seen in all areas. Only the motor cortex, however, was affected to the same extent as in the foregoing case. Here, there was a conspicuous loss of Betz cells with upset of the normal laminated cellular arrangement. Other areas were involved to a much lesser degree and portions of the temporal and occipital lobes were comparatively normal.

Basal ganglia.—Nerve cells in all nuclei showed typical lipid swellings and degeneration.

Brain-stem and spinal cord.—Similar lipid infiltrations were to be seen in nerve cells at all the levels observed (mid-brain, medulla, pons, C.5, D.2, L.4). Fibre tracts were unaltered. A peripheral nerve (sciatic) stained by Weigert-Pal method showed no abnormality.

Cerebellum.—The cerebellum was atrophied as a whole but the vermis was considerably less affected than the lateral lobes which showed great loss of the granular cell layer. Typical swellings on the dendrites and also in the bodies of the Purkinje cells were conspicuous. These cells were much reduced in number and were almost absent in some of the folia. There were no basket fibres around their cell bodies and no climbing fibres were observed in the molecular layer. No swellings were seen on the axons and the white matter appeared normal. Phosphotungstic acid-hæmatoxylin staining showed a marked gliosis in the molecular layer. These changes closely resembled those of the foregoing case.

Retina.—The inner limiting membrane was continuous but undulating in outline. There was a reduction in the number of ganglion cells present and of those remaining many showed ballooning of the cytoplasm and signs of degeneration.

The inner nuclear layer appeared fairly normal, but the outer granular layer and the rods and cones were totally deficient, not only in the neighbourhood of the macula, but extending to the periphery of the retina. Much of the outer plexiform layer had disappeared as well so that the inner nuclear layer was almost in apposition with the pigmented epithelium. These cells were heavily pigmented and showed no signs of degeneration, although in one circumscribed area, proliferation of the pigmented epithelium had taken place. A few histiocytes packed with pigment granules lay in the remnants of the outer plexiform layer, and in clumps around the capillaries in the choroid which appeared unchanged. No abnormalities were noted in the optic nerve.

The changes differed from those in the foregoing case in being much more widespread and in involving the rods and cones extensively, besides the outer nuclear layer and the ganglion cells. The pigmented epithelium was less affected in this case.

Case 4.—B. C., a male aged 18 months. This infant died in an outside hospital, the brain being sent to the National Hospital for diagnosis. The notes available are incomplete but the case is included as the histological changes were typical and provide an interesting comparison with the other cases described.

The patient was first seen at the age of 11 months as an out-patient and was found to be a large, placid infant with congenital nystagmus. His head measured

20 in. in circumference and gave a "cracked-pot" percussion note. He sat up at 8 months and started teething at 10 months, but was considered mentally backward at that age. He retrogressed steadily and died of bronchopneumonia at 18 months of age.

Autopsy.—The liver (275 grammes) and spleen were not enlarged. The kidneys and suprarenals appeared normal. The brain was large for a child of this age and weighed 1,250 grammes. Some of the gyri were considered abnormally firm on palpation.

Histological examination.—Cerebral cortex—in all areas the cytoarchitectonics were fairly well maintained and the inner and outer granular layers demarcated. The pyramidal cells, especially in the deeper part of the third layer and to a lesser extent in the fifth and sixth layers, were infiltrated with lipid which stained a rose-pink with Scharlach. Many cells had undergone degeneration and evoked a glial reaction. Staining by the Victoria Blue method showed a slight increase in fibrous astrocytes throughout the grey matter. Isolated areas in the white matter were undergoing demyelination, staining red with Scharlach. These probably represented changes secondary to the nerve cell degeneration.

Basal ganglia.—The basal ganglia were relatively more involved than the cortex, large, ballooned cells distended with lipid being seen in the caudate nucleus, putamen, globus pallidus, subthalamic nucleus and thalamus. Stained with Scharlach and alum-hæmatoxylin the lipid granules varied in colour from cell to cell from rose-pink to pale orange and even a purplish hue. One area in the internal capsule was undergoing demyelination and stained bright red. Similar changes were noted in the central fibres of the optic tract.

Medulla oblongata.—The cells of the hypoglossal nerve nucleus were diffusely involved; so, too, but less severely, were the cells of the dorsal nucleus of the vagus and the vestibular nucleus. Some of the cells of the facial nerve nucleus were unaffected while others showed slight lipid swellings. The olivary nerve cells were rounded, and filled with lipid stained the same rose-pink as that elsewhere in this section. The pyramidal and other fibre tracts showed no sign of degeneration.

Cervical cord.—The cells of the anterior and posterior horns were equally affected. Scharlach staining showed uneven staining of the lipid in individual large anterior horn cells, the colour varying from pink to purple.

Cerebellum.—The molecular layer appeared normal except perhaps for a slight glial increase and prominence of Bergmann's layer. There was a moderate loss of Purkinje cells, some of which showed "stag-horn" dendritic swellings. Basket fibres were present around many of the cell bodies. The granular layer was not reduced and appeared to be within normal limits. The white matter was unaltered.

Discussion

Biochemical researches have identified the chief lipid in Gaucher's disease to be gluco-cerebrosides (Epstein and Lorenz, 1930) and galacto-cerebrosides (Epstein and Lorenz, 1930; Thannhauser, 1940; Leib, 1924); in Niemann-Pick disease one of the sphingomyelins (Klenk, 1935), and in amaurotic family idiocy one of the sphingomyelins (Tropp and Eckardt, 1936) together with a ganglioside, a phosphatide-free carbohydrate-containing lipid (Walz, 1927). These substances are closely related to one another as both cerebrosides and sphingomyelins arise from the same precursor, lignoceryl-sphingosine (Zehnder, 1937; Thannhauser, 1940).

Reunkamp (1942) has shown that these lipids, in minute quantities, are normal constituents of nerve cells. Only when present in excess do

they cause any harmful effects, and then mechanically rather than by virtue of their chemical composition.

The level of lipids in the blood is within normal limits in each of these diseases (Thannhauser, 1940). This would indicate an error in cellular rather than general lipid metabolism. It is believed that there is an imbalance of the enzymes concerned with lipid anabolism and catabolism within the cell leading to an accumulation of lipid.

Histological investigations confirm that these are diseases primarily of nerve cells. One of the lipids normally present, accumulates in the cytoplasm and occasionally in the axons and dendrites as well, displacing the nucleus to the periphery and causing chromatolytic changes. The neurofibrils are also pushed to the margins of the cells remaining intact and perhaps still functioning, but sooner or later the over-distended nerve cells disintegrate, thus disrupting the neurofibrils. Many appear to burst from mechanical overfilling with lipid. It is this disappearance of nerve cells which is responsible for the development of symptoms. These depend on which area of the brain is most affected. The involvement of nerve cells is widespread, sometimes almost universal. The apparent tendency in certain age-groups for one part of the brain to be affected more than another may be related to the process of myelination which is known to be incomplete at birth and to progress for at least two years thereafter. The myelin, once laid, is not stored statically but is in a state of chemical equilibrium, molecules being constantly added to and removed from the complex. This may account for the ability of the condition to commence at any age. Globus (1942) has stated "variations in the anatomical features are little more than an expression of a stage in the development of the disease. Thus, the presence or absence of inflation of the cell processes, in one or other case, does not alter the basic character of the disease as long as the typical cell-body changes are in evidence. The same holds true for the axis-cylinder changes and for the degree and extent of demyelination."

In areas where nerve cells are undergoing disintegration, compound granular corpuscles are to be seen. They appear to remove the lipid which is left lying intracellularly after destruction of a nerve cell and convert it from being a complex lipid to a simple fat as is shown by Scharlach staining. There is a reaction on the part of fibrous and protoplasmic astrocytes varying according to the site and the extent of nerve cell involvement. In some cases, demyelination may occur in patches in the white matter but these changes are regarded as being subsidiary to those in the grey matter.

The above description applies to the histological changes in all the clinical forms of amaurotic family idiocy. Globus (1942), whose interest in the condition has extended over twenty years, has observed many cases

since his first paper on the subject appeared in 1923. In a recent article he stated "from the foregoing description of the histological findings in the several forms of amaurotic family idiocy, it is quite apparent they constitute variants of the same disease entity. This is well shown by the specific nerve cell changes which serve as the anatomical link between the several variants."

The four cases which have been described above have confirmed this view, not only regarding the infantile and juvenile forms of amaurotic idiocy, but, more important, the juvenile form of Gaucher's disease. In this case the fundamental histological changes were identical with those of amaurotic idiocy. Certain incompatibilities were noted, e.g. the marked cerebellar changes typical of juvenile amaurotic idiocy were present in Cases 2 and 3, but not in the infantile form nor the case of Gaucher's disease; the staining reactions with Scharlach varied in the four cases, but these findings were in keeping with the known biochemical variations between cases. These differences were far outweighed by the features in common.

The binding link between the four cases and the fundamental pathological lesion common to them all is found to lie in the lipid infiltration and associated degeneration of nerve cells. Identical changes have been reported in the central nervous system affected in Niemann-Pick disease (Hassin, 1930; Bielschowsky, 1928; van Bogaert, 1937; Ley, 1940), in the infantile form of Gaucher's disease (Lindau, 1930; Hoffman and Makler, 1929; Moncrieff, 1930), even in gargoylism, a condition superficially remote from those under discussion (Ashby, Stewart and Watkin, 1937). Globus' statement to the effect that the specific nerve cell changes provide the anatomical link between the various forms of amaurotic idiocy may well be extended to include these other conditions as well.

This would seem to justify the introduction of the term *"neuronal lipidosis"* which will not only cover all members of these closely related groups, but will also eliminate the difficulties arising when attempts are made with the clinical nomenclature to classify those cases with anomalous findings (such as amaurotic family idiocy sine amaurosis). It will focus attention on the primary site of the lesion, i.e. the nerve cell and will bring the nomenclature of these conditions on to an anatomical basis, into line with those other anatomical designations of neurology which are eminently satisfactory, e.g. subacute combined degeneration, amyotrophic lateral sclerosis, olivo-ponto cerebellar atrophy, &c.

Tentative Classification of Neuronal Lipidoses

(*a*) Cerebroside neuronal lipidoses associated with cerebroside infiltration of reticular-endothelial cells (Gaucher's disease).

(*b*) Phosphatide neuronal lipidoses: (i) without involvement of reticular-endothelial system (amaurotic family idiocy, &c.); (ii) with involvement of reticular-endothelial system (Niemann-Pick disease).

Summary

Certain of the lipidoses affect the central nervous system—clinical subgroups have been discussed. Four cases have been described, one of Gaucher's disease in a boy of 11 years with nervous system involvement, two of the juvenile form and one of the infantile form of amaurotic family idiocy. The marked similarity between the pathological changes in all these cases has been emphasized and has suggested the term "neuronal lipidosis" as a suitable designation for all members of this group.

Acknowledgment

It is my pleasure to thank my chief, Dr. J. G. Greenfield, who not only provided me with all the material for investigation, but also with help and guidance both during my researches and in the writing of this paper. My thanks are due as well to Dr. Russell Brain for his permission to publish the case of Gaucher's disease and to Dr. M. J. F. McArdle for his permission to publish Case 2 (A. H.).

BIBLIOGRAPHY

Ashby, W. R., Stewart, R. M., and Watkin, J. H. (1937) *Brain*, **60**, 149.
Batten, F. E. (1903) *Tr. Ophth. Soc. U. Kingdom*, **23**, 390.
Bertrand, I., and van Bogaert, L. (1934) *Encephale*, **29**, 505.
Bielschowsky, M. (1928) *J. Psychol. Neurol.*, **30**, 103.
——, and Pick, W. (1927) *Klin. Wchnschr.*, **6**, 1631.
Bloom, W. (1925) *Am. J. Path.*, **1**, 595.
Davidson, C. (1942) *J. Mt. Sinai Hosp.*, **9**, 389.
——, and Jacobson, S. A. (1936) *Am. J. Dis. Child.*, **52**, 345.
Epstein, E. (1924) *Wien. klin. Wchnschr.*, **37**, 1179.
——, and Lorenz, K. (1930) *Ztschr. physiol. chem.*, **192**, 145.
Franco, S., and Wolman, M. (1947) *Schweiz. Z. Path. Bakt.*, **10**, 621.
Giampalmo, A. (1946) *Arch. "E. Maragliano" Patol. Clin.*, **1**, 1.
Globus, J. H. (1942) *J. Mt. Sinai Hosp.*, **9**, 451.
Greenfield, J. G., and Holmes, G. (1925) *Brain*, **48**, 183.
——, and Nevin, S. (1933) *Tr. Ophth. Soc. U. Kingdom*, **53**, 170.
Grinker, R. R. (1927) *Arch. Path.*, **3**, 768.
Halliday, N., Deuel, H. J., Jr., Trageman, E. J., and Ward, W. E. (1940) *J. Biol. Chem.*, **132**, 171.
Hassin, G. B. (1930) *Arch. neurol. Psychiat.*, **24**, 61.
Hoffman, S. J., and Makler, M. I. (1929) *Am. Jour. Dis. Child.*, **38**, 775.
Hurst, E. W. (1925) *Brain*, **48**, 1.
Klenk, E. (1935) *Ztschr. physiol. chem.*, **235**, 24.
Knox, J. H., Wahl, H. R., and Schmeisser, H. C. (1916) *Bull. Johns Hopkins H.*, **27**, 1.
Kohne, G. (1938) *Beitr. path. Anat, allgem. Path.*, **102**, 3.
Kufs, H. (1928) *Ztschr. Neurol. Psychiat.*, **117**, 753.

PLATE XXII

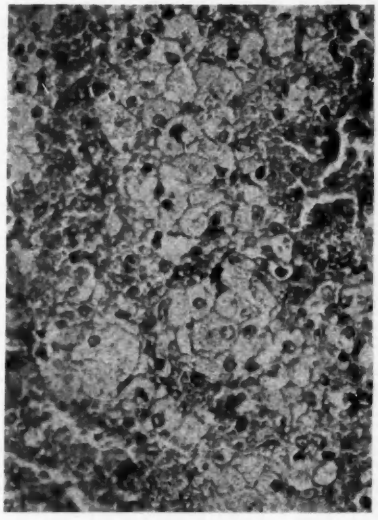


FIG. 1

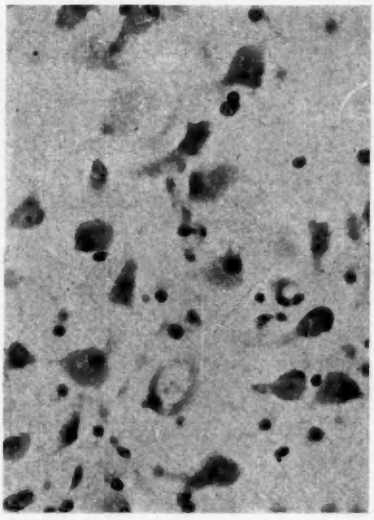


FIG. 2

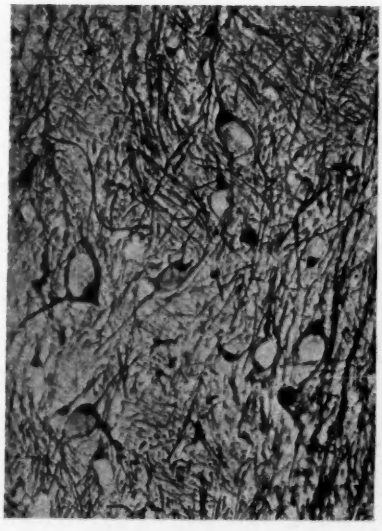


FIG. 3

FIG. 4

To illustrate article by Alan Bird.

PLATE XXIII

FIG. 5

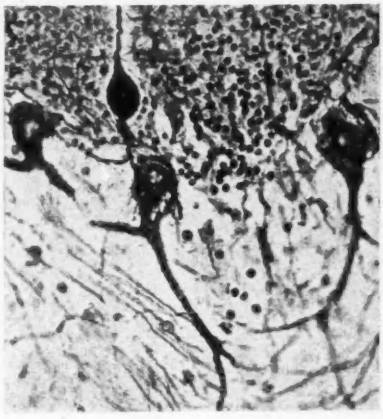


FIG. 6

FIG. 7

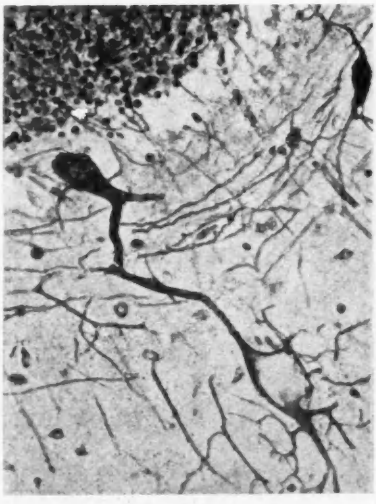


FIG. 8

To illustrate article by Alan Bird.

PLATE XXIV

FIG. 9

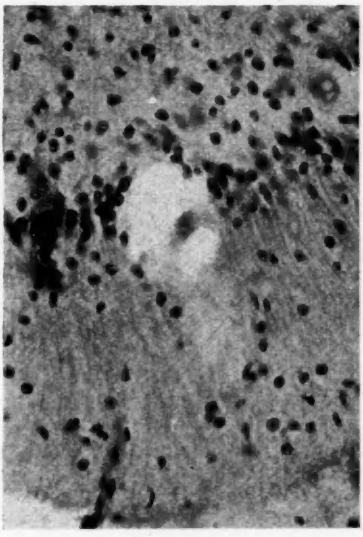


FIG. 10

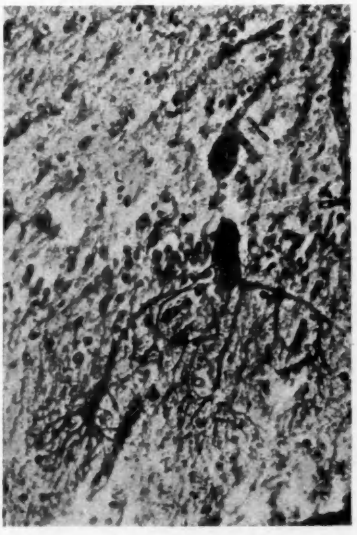


FIG. 11

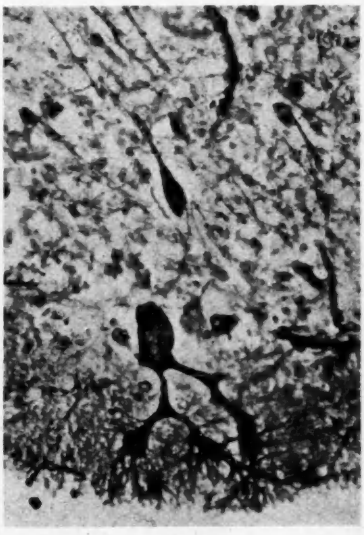


FIG. 12

To illustrate article by Alan Bird.

PLATE XXV

FIG. 13

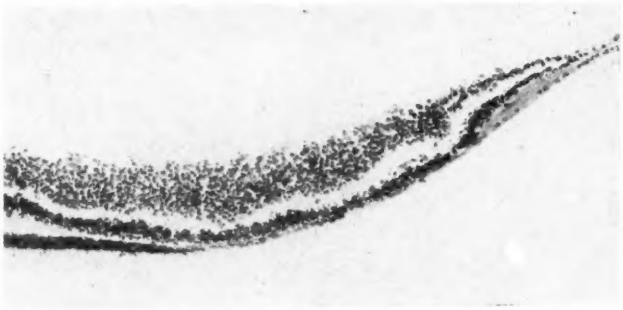


FIG. 14

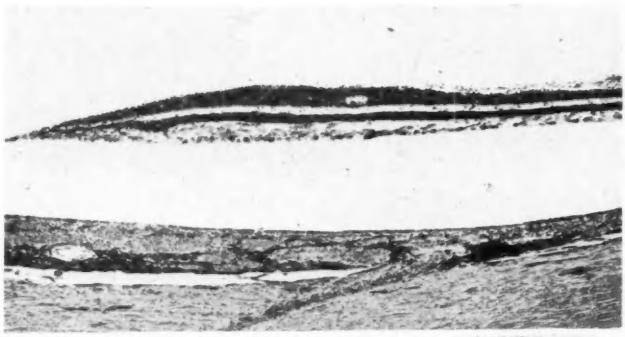
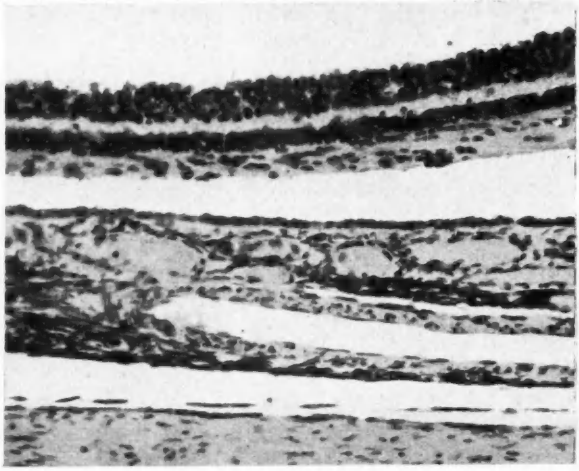


FIG. 15



To illustrate article by Alan Bird.

LEY, R. A. (1940) *J. Belge Neurol. Psychiat.*, **2**, 57.
LIEB, H. (1924) *Ztschr. physiol. chem.*, **140**, 305.
LINDAU, A. (1930) *Acta psychiat. neurol.*, **5**, 167.
MONCRIEFF, A. (1930) *Arch. Dis. Child.*, **5**, 265.
NORMAN, R. M., and WOOD, N. (1941) *J. Neurol. Psychiat.*, **4**, 175.
OBERLING, C., and WORINGER, P. (1927) *Rev. franc. Pediat.*, **3**, 475.
REUNKAMP, F. (1942) *Ztschr. physiol. chem.*, **272**, 280.
ROWLAND, R. S. (1931) *Oxford Med.*, 4.
RUSCA, L. C. (1921) *Hæmatologica*, **2**, 441.
SACHS, B. (1887) *J. Nerv. and Ment. Dis.*, **14**, 541.
TAY, W. (1881) *Tr. Ophth. Soc. U. Kingdom*, **1**, 155.
THANNHAUSER, S. J. (1940) Lipidoses: Diseases of the Cellular Lipid Metabolism. O.U.P.
TROPP, C., and ECKARDT, B. (1936) *Ztschr. physiol. chem.*, **243**, 38.
VAN BOGAERT, L. (1937) *Pr. med.*, 31 - 27.
——, and FROHLICH, A. (1939) *Ann. Med.* **45**, 57.
WALTER, F. K. (1918) *Ztschr. Neurol. Psychiat.*, **40**, 349.
WALZ, E. (1927) *Ztschr. physiol. chem.*, **166**, 210.
WYBURN-MASON, R. (1943) *Br. J. Ophth.*, **27**, 145.
ZEHNDER, M. (1937) *Klin. Wchnschr.*, **16**, 553.

LEGENDS FOR ILLUSTRATIONS

PLATE XXII

FIG. 1 (*Case* 1).—Section of spleen showing masses of foamy "Gaucher" cells.

FIG. 2 (*Case* 1).—Cerebral cortex, showing varying degrees of lipid accumulation in the neurons, some being almost normal, others very degenerated. Thionin stain for Nissl granules.

FIG. 3 (*Case* 1).—Globus pallidus. In this area the cell bodies of all the nerve cells are distended with lipid, which has pushed the neurofibrils to the periphery. Da Fano-Bielschowsky silver impregnation.

FIG. 4 (*Case* 1).—Anterior horn of spinal cord, showing variable degrees of lipid accumulation in the motor neurons. Da Fano-Bielschowsky silver impregnation.

PLATE XXIII

FIGS. 5 to 8 (*Case* 1).—Cerebellar cortex stained by Bielschowsky's silver impregnation and showing varying degrees of degeneration of the Purkinje cells. In fig. 5 there is a star-shaped swelling on the dendrites and in figs. 7 and 8 more irregular antler-like swellings. An axonal swelling "torpedo" is seen in fig. 6. Note that basket fibres are absent in figs. 5 and 8 but present in figs. 6 and 7.

PLATE XXIV

FIG. 9 (*Case* 2).—Low-power view of cerebellar cortex showing almost complete disappearance of granule cells, and paucity of Purkinje cells. One of the latter is in the process of bursting from lipid distension.

FIG. 10 (*Case* 2).—Same area of cerebellar cortex under higher magnification, to show the details of the disintegration (bursting) of the Purkinje cells. Note also the palisaded line of Bergmann astrocyte nuclei.

FIG. 11 (*Case* 2).—Cerebellar cortex stained by Bielschowsky's silver technique. The body of the Purkinje cell has a clear area containing lipid, there is an axonal torpedo and plume-like swelling of the dendrites.

FIG. 12 (*Case* 3).—Cerebellar cortex stained by Bielschowsky's silver technique. The appearances here are altogether comparable with those in fig. 11. There is

atrophy of the granular layer, and axonal cytoplasmic and dendritic swellings in the Purkinje cell shown.

PLATE XXV

FIG. 13 (*Case* 2).—Section of retina for 1·5 mm. from the fovea centralis. For the inner 1 mm. the outer granular layer is deficient and some pigment has migrated here from the pigmentary epithelium.

FIGS. 14 and 15 (*Case* 3).—Section of retina under lower and higher power than fig. 13. The outer granular layer here is totally absent and there is rather more migration of pigment from the pigmentary epithelium, which otherwise remains intact. There is very little swelling of the cytoplasm of the nerve cells in either Case 2 or Case 3.

SARCOIDOSIS WITH INVOLVEMENT OF THE NERVOUS SYSTEM

BY

J. COLOVER

(From the National Hospital, Queen Square, London)

SINCE the recognition of the disease entity of sarcoidosis, or Besnier-Boeck-Schaumann disease, there has been a considerable number of cases reported in which the nervous system has been involved. This paper contains a survey of 115 such cases, and reports three further cases admitted to the National Hospital, Queen Square, London.

The earliest descriptions of the disease in which the involvement of the nervous system was recognized are those of Winkler (1905), Mazza (1908), Heerfordt (1909) and Urban (1910). Winkler, Mazza and Urban all described the pathology of the lesions in the peripheral nerves. Heerfordt described three cases of his own and collected a number from the literature under the title of "febris uveo-parotidea subchronica" which is now established to be a particular variety of the disease.

Recent reviews which have stressed the neurological aspects of this disease are those of Ernsting and Sillevis Smitt (1944), Hantschmann (1939), Levin (1935), Ottonello and Anardi (1940), Pautrier (1940), Roos (1938), Savin (1934) and Toulant and Morard (1936).

The disease has to be differentiated from temporal or giant cell arteritis, epidemic parotitis, Hodgkin's disease, torula infection, leprosy, syphilis and tuberculosis.

There has been considerable controversy regarding the ætiology of this disease, but the majority of observers hold the view that it is an atypical form of tuberculosis. The most recent discussions regarding the ætiology are those of Hoyle (1947), Freudenthal (1948), Pautrier (1948) and Michelson (1948). It will be seen that, although any part of the nervous system may be affected by the disease, there are certain sites which seem to be particularly vulnerable, and it may be that the explanation of these facts may throw light on the question of the ætiology of the disease. It is also possible that when the problem of the ætiology is finally solved, it will, in the light of these facts, provide further information about the nervous system. Therefore the neurological manifestations of the disease are of more than intrinsic interest.

CASE HISTORY (1)

Mrs. D. M. S., aged 30, was admitted to the National Hospital, under the care of Dr. MacDonald Critchley, June 16, 1939.

She complained of painful swelling of both parotid regions of her face for twenty-three days, paralysis of the left side of her face for seven days, and weakness of the right leg for one day.

Family history.—There was no history of tuberculosis.

Previous health.—She had not had mumps, nor any chest complaints.

Present illness.—Towards the end of 1938, after a period of close contact with a case of open pulmonary tuberculosis, she began to feel run down. This feeling of ill-health persisted and was worse after a minor pelvic operation in May 1939. In eight months she had lost 12 lb. in weight.

On May 21 she started to have severe headache, situated over the forehead and behind the eyes, which persisted. She felt generally unwell and went to bed for a day. Three days later on waking up in the morning she noticed a small painful lump in the left parotid region. Her vision was misty, her eyes smarted and she could not bear strong light. About June 6 the right parotid gland also became painful and swollen. Both glands steadily increased in size and were the location of throbbing pain, which was particularly troublesome at night. She felt ill and had a fever. On June 8 the left side of her mouth felt weak and she was unable to close the left eye. At that time she was unable to taste food normally in the left side of her mouth and the following day the facial weakness became extreme and she could taste only slightly in the right side. Her sense of taste had improved slightly subsequently. Describing her sense of taste she said that cocoa had no taste at all, fruit flavours were only partly recognizable and were distorted. Sweets were unpleasant. Chocolates were a "tasteless mess." Tea tasted like tea.

For two or three days preceding the loss of taste she had the impression that there was a thick sticky fluid exuding from a point in her left cheek.

On May 29 the lower part of her abdomen had felt uncomfortable and tender. This had persisted.

On June 16, the day of admission, she noticed weakness of the right leg when walking. She had always been subject to cramp in the legs at night and these had not altered since the onset of her illness.

There was no diplopia, no dysphagia, no hyperacusis, no rash, and no cough.

State on examination.—She was mentally alert. Physically she was well nourished. Her mouth was dry but uninfected. Her tongue and pharynx were healthy.

Parotid glands: There was a smooth uniform firm generalized swelling of the left parotid gland including the retroauricular lobe. The right parotid gland was slightly enlarged. Both glands were tender.

Eyes: There was a small tag in the inferior margin of the left pupil and the media were a trifle hazy. There was evidence of iridocyclitis under magnification with a hand lens.

Cranial nerves: (1) There was no anosmia.

(2) The visual acuity was 6/12, right and left. The visual fields were full. The fundi were normal, through slightly cloudy media.

(3, 4 and 6) The pupils were of moderate size, the right smaller than the left. They reacted briskly to light and convergence.

(7) There was almost complete loss of movement of the left side of her face. The left eyelid moved but the eye could not be closed. Taste: this was imperfectly appreciated on both sides of the tongue, the left being worse than the right. The remaining cranial nerves were normal.

Motor system: The lower limbs were rather weak, especially on the right where there was weakness of flexion of the thigh and all movements of the knee and ankle. There was no atrophy although the patient said that her legs had become very thin. Tone and co-ordination were normal. The arms and trunk were normal.

Sensation: All forms were normally appreciated.

Reflexes: Her triceps, biceps, and supinator reflexes were normal. Her right

knee-jerk was diminished compared with the left. Her ankle-jerks were equal and present. Her lower abdominal reflexes were absent. Her plantar reflexes were flexor.

Her gait was slow and hesitant, with unsteadiness to both sides. She could curtsey with the weight on her left leg, but not on the right. Rombergism was absent.

Cardiovascular system: Normal apart from a distinct third sound at the apex.

Chest: This was normal to clinical examination.

Abdomen tender and rather rigid. Nothing abnormal was felt.

Clinical course.—On June 19, three days after admission, the right face became weak. She was unable to close the right eye and movement of her mouth and of facial expression became deficient. The next day the paralysis of the left face was almost total. No hyperacusis was present. She had some pyrexia. Two days later the eyes became less painful and the photophobia diminished. She began to complain of "pins and needles" on the anterior and medial aspects of her right thigh. Her abdominal reflexes were now all absent, and the right knee-jerk was reduced, although there was no increase in the weakness of her right lower limb.

On June 26 her right knee-jerk was absent and her right triceps-jerk was diminished. At this time her taste began to return. On June 28 she complained that in brushing her lower front incisor teeth, it felt as if the nerves were exposed. The parotid glands were less painful now, and some movement of the angle of the mouth on the right had returned. There was hypalgesia to pin-prick below the right elbow and below both knees, more marked distally. Cotton-wool was felt everywhere.

In the next fortnight her eyes, facial movement, and taste sensation improved. The right parotid gland enlarged still further, although movement of the right face became normal. Her left knee-jerk became very sluggish.

On July 19 she developed a rash on the inner side of both ankles, above and below her internal malleoli. There were scattered bluish-pink lesions, about half a centimetre in diameter, slightly indurated, not tender. Her spleen was just palpable at this time. Within a few days the rash faded and the spleen became impalpable. Her taste improved and became normal. She had some pyrexia and complained of a dull aching pain in her right wrist and knee. Her right triceps and knee-jerks reappeared on July 31. Her eyes became normal apart from slight corneal opacity.

Investigations.—Radiologically her chest was normal. Her sedimentation rate was raised to 24 mm. (modified Westergren, 100 mm.). Her Mantoux reaction was positive to 1:1,000.

She was discharged on August 11, 1939.

Summary

A woman aged 30, after a period of five months during which she felt unwell and lost weight, developed bilateral iridocyclitis and parotitis, followed by bilateral facial paralysis and ageusia. She had a mild irregular pyrexia. Her legs became weak and she lost her abdominal reflexes and some of the tendon reflexes in her lower limbs. Her spleen enlarged and she developed a transient rash on her legs. She had hypalgesia below both knees and below the right elbow.

This patient showed uveo-parotitis with polyneuritis. The loss of taste was an unusual but recognized feature of this syndrome. It was interesting to note that the right facial paralysis was improving although the right parotid gland was still enlarging, which would indicate that the

paralysis was not due to direct pressure of the parotid gland on the facial nerve. The loss of taste also supports this view.

CASE HISTORY (2)

H. A., an unmarried pharmacist, aged 56, was admitted to the National Hospital under the care of Dr. J. Purdon Martin on August 13, 1927.

Family history.—A brother and sister had died of diphtheria.

Previous health.—Sciatica twenty years previously, syphilis in his youth—his blood Wassermann reaction six weeks prior to admission had been negative.

Present illness.—He complained of swelling of the right side of the neck and weakness of the face and shoulders.

Eight months before admission, in January 1927, he noticed that his tongue was furred and white in the mornings, associated with an unpleasant taste in his mouth. At the same time he noticed a small lump in the right side of his neck and soreness just above the right clavicle. Two months later the shoulder and back felt stiff. In April the right knee-joint felt frozen and aching, and this aching extended above and below the patella. About a month later there was a similar cold patch in the interscapular region. Early in June he woke one morning to find that the left side of his face was flat, and the mouth was twisted to the right. In a few days the face seemed to correct itself, but a patch of coldness appeared over the left mastoid process.

Six weeks before admission the right face seemed to become weak, and five or six days later he had severe pain radiating from behind the ear, into the ear and temple. The face seemed to get better before the pain came on.

For a month he had felt some stiffness in his throat and a vague difficulty in swallowing and this had become more pronounced in the last fortnight. He could swallow fluids quite well provided that he drank slowly, but the fluid regurgitated from his nose if he tried to gulp it down. Solids appeared to stick at the back of his throat. He found difficulty in swallowing his saliva which appeared to be excessive although it did not trickle from his mouth. He had some difficulty in talking and in pronouncing the vowels O and U. He was unable to express his emotions with his face. He had some difficulty in hearing those who did not speak distinctly. There was no vertigo or tinnitus.

For three months prior to admission there had been some frequency of micturition. For one week his toes had been painful.

State on examination.—The patient was a well-built man, his face was smooth and pale. He looked rather solemn and sullen and when laughing there was just the slightest movement in the lower lip. He was intelligent and co-operative. There was slight dysarthria especially with the labio-dentals and vowels.

There was some lachrymation and conjunctivitis of the right eye.

The head gave the appearance of having been sunk between the shoulders, and there was a fairly well-marked thoracic kyphosis.

Cranial nerves: (3, 4 and 6) The left pupil was slightly larger than the right, the reactions and shape were normal.

(7) There was a bilateral facial paralysis affecting both the lower and upper face. The skin of the forehead was smooth; he was unable to frown; on attempting to close the eyes, movement in the orbicularis oculi was very slight and the eyeballs rolled upwards. Few contractions were observed in the orbicularis oris and only slight movement in the left upper lip.

Taste: The tongue was covered with heavy white fur; salt, acid and quinine could not be tasted on either side with the tongue protruded, and sugar could only be tasted on the left. All these substances could be instantly recognized on withdrawing the tongue into the mouth.

(8) Deafness was present on the right side.

(9 and 10) The soft palate hung lower than normal and was flabby. The left side of the palate moved better than the right, palatal elevation caused the uvula to be drawn over to the left. There was no movement of the right vocal cord. There was dysphagia with frequent nasal regurgitation.

(11) The right sternomastoid did not contract, the left contracted moderately well. Both trapezii were wasted and weak, the right more than the left.

(12) The tongue though moist was covered with a thick white fur. On pushing the tongue into the cheek there was marked weakness, the left side more than the right No atrophy or fibrillation was present.

Motor system—Arms: The musculature was flabby, and power was poor on both sides, the right being weaker than the left. Movements of the right shoulder, elbow, wrist and fingers were feeble. *Lower limbs*: There was some general wasting and the musculature felt flaccid. Power here was fair, the left being better than the right. The weakness on the right was more marked for ankle and foot movements.

Reflexes: The knee-jerks were sluggish, and the ankle-jerks were absent. The arm-jerks were present.

Skeletal system: There was a well-marked thoracic kyphosis and arthritis of both knees. The right mastoid process was tender on deep pressure.

Alimentary system: The right tonsil was swollen and septic. The liver edge could just be felt on deep respiration.

Lymphatic system: There were enlarged discrete lymph nodes in the posterior triangle on the right side. Near the apex of the triangle were two larger swellings the size of bantam's eggs. They were not tender, or fluctuating and were not attached to the overlying skin.

Clinical course.—His temperature occasionally rose to 99·4° F. in the evenings, and his pulse-rate was mainly between 88 and 100 per minute occasionally rising to 110. One week after admission he developed a right superior oblique paresis, and also he had wasting of his right triceps brachialis and right deltoid. The following day he developed a right 3rd nerve paralysis. His left ankle-jerk could just be elicited. He was vomiting occasionally. His right arm began to have increased power at this time. Six weeks after his admission his optic disc margins became blurred. Two months after his admission the face began to improve and a hard irregular swelling was noticed in his right supraspinous fossa. A week later his left external rectus became weak.

He received radiotherapy to the glands in his neck and he was discharged twelve weeks after admission, his condition having improved.

The following special investigations were performed on him:

Radiological investigation.—His spine showed marked scoliosis in the dorsal region and also arthritic changes. He had an unusually pulsatile aorta with broadening of the aortic and superior mediastinal shadows, with evidence of calcified mediastinal glands.

Otological examination.—The deafness was of middle-ear type.

Lumbar puncture (18.8.27).—The fluid was clear and colourless; 26 cells per c.mm. practically all small lymphocytes, about 2 per cent. large mononuclears. Total protein 0·10 gramme per cent., Nonne-Apelt positive (+), Pandy positive (++), Lange 1111221100. Wassermann reaction negative in cerebrospinal fluid and blood.

Biopsy of a cervical lymph node was carried out and the sections stained with hæmatoxylin eosin, and hæmatoxylin van Gieson's stain. They showed (fig. 1) numerous rounded circumscribed collections of pale staining endothelioid cells, surrounded by lymphocytes. These collections of cells tended to be aggregated together to form larger lesions. Numerous giant cells were present, many being of the Langhans type with a ring of nuclei lying in the periphery of the cell.

A few had their multiple nuclei more evenly distributed throughout the cell cytoplasm. No caseation or necrosis was present.

Summary

A man aged 56 had enlarged cervical glands, and a disturbance of taste for eight months. During this time he complained that certain patches of his skin felt cold and frozen. He then developed bilateral facial paralysis, difficulty in swallowing, weakness of the palate, and paralysis of the right vocal cord. The trapezii were weak and wasted and the tongue was weak. He had weakness of his upper and lower limbs. His knee-jerks were sluggish, his ankle-jerks absent. The margins of his optic discs became blurred, and he developed paresis of some of his external ocular muscles. He had a hard irregular swelling in his right supraspinous fossa. His temperature occasionally rose in the evenings to 99·4° F.

Although the disturbance of taste in this man was associated with furring of his tongue, to which it might well be attributed, this symptom is reminiscent of the previous patient and also of other cases in the literature in whom this feature was recorded. Similarly in other recorded cases there have been complaints of patches of skin which felt "frozen."

The histological examination of an excised cervical gland showed typical sarcoid tissue.

The case presented itself as a polyneuritis with involvement of cranial nerves. It is interesting to note the occurrence of bilateral facial paralysis of the peripheral type without parotitis being present.

Discussion

One hundred and fifteen cases which showed involvement of the nervous system have been collected from the literature. With the 2 cases previously described and the case to be described later on, they form a series of 118 cases. The youngest patient in the series was that described by Naumann (1938) whose age was three months.

The following table gives the frequency of some of the associated features recorded in these cases.

	No of cases.	per cent.
Parotitis	73	62
Iridocyclitis	67	56
Pyrexia	44	37
Cutaneous lesions	33	28

Cranial Nerve Lesions

In 58 cases there was facial paralysis of the peripheral type, so that about 50 per cent. of cases have facial paralysis. It was unilateral in 36 cases, and bilateral in 22 cases. Facial paralysis may occur in the absence of

parotitis, as recorded by Ford (1945) and as also occurred in the second patient previously described. When the facial paralysis is bilateral, the interval between the onset of paralysis on the two sides is a matter of days, but this period occasionally may be many months. Usually the facial paralysis clears up completely, but facial contracture has been described twice (Macbride, 1923; and Rothfeld, 1930). Facial spasm was described by Ottonello and Anardi (1940). 10 cases with facial paralysis also had loss of, or disturbance of, taste. Occasionally the taste disturbance preceded the facial paralysis, as in the case described by Meissner (1938).

The next most frequently involved cranial nerve was the optic nerve. The pathology of lesions of the optic nerve was described by Pautrier (1938) and others.

In 16 cases definite swelling of the optic disc was observed, usually up to 1 dioptre of swelling. In one patient described by Reis and Rothfeld (1931) there was a tumour in the optic nerve that caused 20 dioptres of swelling. In 10 other cases the optic disc showed hyperæmia, blurring of the disc margins, or engorgement of the veins. Retrobulbar neuritis was mentioned by Longcope (1941) as occurring in one case; Souter (1929) and Meyer (1938) each recorded a case with a central scotoma. Optic atrophy was described by Dor (1900) and Ramsey (1921). 4 cases showed choroido-retinitis. Other retinal lesions described were neuro-retinitis, Kuhlefeldt (1917), perivasculitis, von Bahr (1938), and choroidal atrophy.

The next most frequent lesion was involvement of the pharynx, soft palate and vocal cords. 29 patients had difficulty in swallowing food. Many had nasal regurgitation and paralysis of the soft palate, the latter often being more marked on one side. 9 cases showed paralysis of one or both vocal cords, again more frequently unilateral than bilateral. One case showed loss of heat sensibility of the pharynx (Schüpbach, 1936).

Nerve deafness was noted in 8 cases, and in 4 cases there was disturbance of the vestibular branch of the acoustic nerve.

Six cases showed ptosis, usually slight. In 3 patients paralysis of the 3rd nerve was present. 6th nerve paralysis was present in the cases described by Revilliod (1896) and Harrell (1940). The only case recorded in which there was a paralysis of the 4th nerve is Case 2 in this paper.

Owing to the frequent occurrence of iridocyclitis it is rather difficult to assess the pupillary anomalies that may be present. In 3 cases the pupils were described as sluggish in the absence of active iritis. In one case the pupils reacted feebly to light but not to convergence-accommodation (Critchley and Phillips, 1924). Pupils that were immobile to light but which reacted to convergence were recorded by MacKay (1921). Cycloplegia was recorded by Dopter (1904) and Tait (1934).

Sensory loss or impairment in the trigeminal area of the face was described in 5 cases (Ramsey, 1921; Schüpbach, 1936; MacBride, 1923; Levin, 1935; and Thompson, 1937). In the case described by Levin the loss was bilateral and the tip of the tongue was numb. Loss of touch sensation over one-half of the tongue was recorded by Schüpbach (1936). Weakness of the muscles of mastication was described by Rothfeld (1930) and Ottonello and Anardi (1940). Diminution or loss of corneal reflexes was noted in 3 cases and corneal anæsthesia was recorded by Meissner (1938).

In 7 cases the tongue showed weakness, usually deviating to one side on protrusion. Atrophy and fibrillation of the tongue were described by Rothfeld (1930).

2 cases had anosmia which developed whilst they were under observation (Thompson, 1937; Lesné, Coutela and Levesque, 1936).

Apart from the second case recorded in this paper, the only other case in which there was paralysis of the muscles supplied by the spinal accessory nerve was that of Revilliod (1896).

Lesions of Peripheral Nerves

The pathology of these lesions was described by Mazza (1908), Winkler (1905) and Urban (1910). In the case described by Mazza there were spindle-shaped swellings of the median, radial, and ulnar nerves. The cutaneous nerves of the left ring finger showed nodular thickening. The nerves involved were irregular in calibre. Histologically there were lesions composed of endothelioid cells, lymphocytes, mononuclears, plasma cells and giant cells between the nerve fibres, many of which were disrupted. The only intact fibres in the nerve trunks involved were those in the periphery of the nerves.

Boeck (1916) described a case in which there was thickening of the left ulnar nerve associated with anæsthesia in the territory supplied by this nerve, and also Heerfordt (1909) described a case in which there was a disturbance of sensation in the ulnar borders of the hands.

Intercostal neuritis.—Pain in the area supplied by intercostal nerves or sensory disturbances in the same area with loss of the corresponding abdominal reflexes was present in the cases described by Heerfordt (1909), Ramsey (1921), Waldenström (1937), and Ernsting and Sillevis Smitt (1944, Case 2).

In Table I are summarized the main findings in 21 cases that showed symptoms or signs of peripheral nerve involvement. A small number of cases in which there were only paræsthesiæ have not been included in this table.

Pituitary and Hypothalamic Lesions

Tillgren (1935) and Schaumann (1936) described a case that came to autopsy in which the pars intermedia of the pituitary gland was invaded by nodules of sarcoid tissue. Polydipsia was the first symptom of the illness and preceded other symptoms by one year.

Polydipsia and polyuria were present in 20 cases. In a further 2 cases only excessive thirst was noted. Levin (1935) and Flandin, Parat, and Paumeau-Delille (1936) respectively recorded cases with a daily fluid intake and urine output of 15 litres, but the average was considerably less than this.

Diabetes insipidus associated with obesity and hypogonadism was described by Francheschetti and De Morsier (1941). Doub and Menagh (1929) recorded a case that showed Fröhlich's syndrome. Infantilism was recorded by Haas and Joseph (1908) and Toulant and Morard (1936). In the case reported by Coleman and Meredith (1940) the sella turcica showed enlargement and bitemporal hemianopia was present.

Amenorrhœa has been recorded by numerous authors.

In 6 cases there was marked hypersomnia or lethargy and on account of this at least one patient was suspected to be suffering from encephalitis lethargica. Guillain (1922) described a case in which the desire for sleep was irresistible. Involvement of the hypothalamus as an autopsy finding was recorded by Longcope (1941).

Cerebrospinal Fluid

A slight pleocytosis was noted in one patient by Heerfordt in 1909 and in the series under review there were 23 other cases in which an abnormal cerebrospinal fluid was found. 17 of these have been tabulated in Table II. The commonest abnormalities are a pleocytosis, an increase in globulin, and an increase in protein. The cells present are usually lymphocytes, but very occasionally small numbers of polymorphonuclear leucocytes are present. The highest cell count recorded is 162 cells per c.mm. The highest protein recorded was in the fifth case of Ernsting and Sillevis Smitt (1944) with 0·720 gramme per cent. This fluid also showed xanthochromia. There is no constant relationship between the pleocytosis and the amount of protein. The pressure of the cerebrospinal fluid may be raised.

Meningeal Involvement

Subacute lesions. Naumann (1938) described a 3 month-old infant with hepatomegaly and splenomegaly. The skin of the abdomen and genitalia showed an eruption of oval dark-red infiltrated areas, and there were petechial hæmorrhages on the neck. A severe anæmia was present. The infant developed convulsions and was found

to have neck rigidity. The cerebrospinal fluid pressure was raised and there was a marked pleocytosis, most of the cells being lymphocytes. There was a pyrexia. The tendon reflexes were lost and the infant died after six weeks. At autopsy there were typical sarcoid lesions in the subdural layer of the falx, in the tentorium cerebelli, and under the sutures of the skull. Both the pachymeninges and leptomeninges were infiltrated.

Chronic meningitis, arachnoiditis, and hydrocephalus.—Sicard (1914) reported a boy aged 15 with marked hydrocephalus. He had pallor of both optic discs, nystagmus, intention tremor and scanning speech, and a spastic quadriplegia. There were no sensory symptoms or sphincter disturbances. His illness had commenced with parotitis two years earlier which in a few days had been followed by a meningitis with a lymphocyte increase in his cerebrospinal fluid. The meningeal signs were followed by headaches and vertigo. Over a period of two years he became obese and developed hydrocephalus. As there is no other case recorded in the literature in which infective parotitis was followed by chronic hydrocephalus it seems more probable that the hydrocephalus and the parotitis were due to sarcoidosis.

Uthoff (1912) reported a case which he regarded as a case of healed tuberculous meningitis. It was associated with bilateral enlargement of the parotid glands, bilateral iridochoroiditis, and a "tuberculous" affection of the apex of one lung. The patient complained of headache and vertigo, and showed nystagmus, facial paralysis and ataxia. The cerebrospinal fluid pressure was increased.

Under the heading of "Ueber seltene, sehr chronische verlaufsform tuberkulöser meningitis" Strasman (1911) recorded a patient who for many years had suffered from "bad eyes." For ten years he had an eruption on his face which was regarded as lupus erythematosis but which histologically was like tuberculosis without caseation. He began to put on weight, became drowsy and easily fatigued. He lost his libido and became impotent. After two and a half years he began to have severe headaches and was found to have optic atrophy and bitemporal hemianopia. His condition deteriorated over the course of a further year during which time he was afebrile. He was then explored and died thirteen days after exploration from a streptococcal meningitis. At autopsy apart from a recent suppurative meningitis, the pia-arachnoid was infiltrated by follicular lesions made up of mononuclears, epithelioid cells and giant cells. The optic chiasma was surrounded by the same tissue which had also invested the optic nerves. Accompanying the blood vessels was similar tissue. There was no caseation or necrosis, and hæmorrhages and thromboses were also absent. Although the author isolated two curved rods by means of a sedimentation preparation, which he regarded as

tubercle bacilli, the skin lesions, the long afebrile course of the illness, and the histological findings are much more in favour of the diagnosis of sarcoidosis.

Simons and Merkel (1917) described a woman of 24 who suffered from lupus pernio. She had a history of amenorrhœa for two and a half years, weakness of the legs for just under eighteen months and headaches for one year. Then during a period of six weeks prior to death she developed severe headache, vomiting and polydipsia. Her face became very swollen, her pupils became fixed to light, she developed facial weakness and transient nasal speech. She had nystagmus on lateral deviation of her eyes. Also she had vertical nystagmus which was brought on by looking upwards or by extending the neck. She showed diminution of her corneal reflexes and developed a convergent strabismus. Her legs were weak and showed sensory disturbances, loss of tendon reflexes, and bilateral extensor plantar reflexes. In addition she had a catarrhal lesion at the apex of one lung, enlargement of the spleen and lymph nodes. Eighteen months after the weakness first appeared in her legs she died. At autopsy the brain showed internal hydrocephalus. There were inflammatory lesions involving the wall of the 3rd ventricle and there was similar granulation tissue surrounding the optic nerves and optic chiasma. The pituitary gland was infiltrated. The cerebellum was adherent to the calamus scriptorius. The meninges in the neighbourhood of the 5th and 7th nerves were infiltrated and this infiltration extended into the epineural connective tissue. The spinal dura mater was studded with small lesions on its inner aspect and the spinal leptomeninges were thickened and infiltrated. The infiltrating tissue was made up of tubercles composed of lymphoid cells, lymphocytes and Langhans' giant cells. The perivascular spaces were filled with a thick layer of fibrils and round cells. The spinal cord showed degenerative changes which were most marked in the posterior lateral columns. No caseation, hæmorrhages or thromboses were present. No tubercle bacilli were ever isolated. Although the lung did show an old tuberculous lesion, the clinical features, the presence of lupus pernio, the long length of history, and the histological findings are very much in favour of the diagnosis of sarcoidosis.

Two cases of sarcoidosis in which the meninges were involved were reported by Longcope (1941).

Erickson, Odom, and Stern (1942) reported a case of meningo-encephalitis, due to sarcoidosis, which came to autopsy. Their patient had a sarcoid lesion on the upper lip and developed the symptoms of raised intracranial pressure. A posterior fossa exploration revealed a chronic adhesive arachnoiditis with herniation of the cerebellar tonsils through the foramen magnum. Examination of the thickened pia-

arachnoid after death showed it to be infiltrated with round cells, endothelioid cells, plasma cells and Langhans' giant cells. The cerebrospinal fluid showed an increase of protein and a pleocytosis.

Recently the following case was admitted to the National Hospital and the findings in many respects were similar to the case reported by these authors.

Case History (3)

Mrs. J. E. P., No. 2970, aged 23, was admitted from out-patients to the National Hospital, under the care of Sir Charles Symonds, on March 31, 1947.

She complained of headaches for the past nine months, nausea and vomiting for the past three months.

Family history.—Nothing of significance.

Previous health.—At the age of 9 she had sustained a head injury, which was followed by two "black eyes." She had not been concussed, and there were no headaches subsequently. In the past she had only slight headaches occasionally. Five months before the onset of her present symptoms she had a right nephrectomy performed at another hospital for renal calculi, after complaining of pain in the right loin for three months. The pathologist's report on the kidney which was removed stated that it showed the presence of large numbers of calculi. Sections of the organ showed destruction and fibrous tissue formation resulting from the presence of the calculi. Round-celled areas were also prominent. There was no evidence of malignancy.

Present illness.—In July 1946 she began to get headaches, which were intermittent. The headache began behind the left eye and spread to the left side of the head. It was generally a dull ache but was punctuated by momentary sharp pains. It usually began in the mornings and was quickly relieved by aspirin. It came on nearly every other day. After three months the headaches became much less frequent and less severe, and the periods of freedom from headache sometimes lasted as long as two weeks.

In early January 1947, the headaches began to occur daily. They were more severe than at the onset, although the stabbing quality was absent. The pain commenced now with gradual aching at the back of the neck and spread as a dull ache all over the head, but was felt chiefly behind the left eye. Whilst the headache was on, the neck felt stiff and uncomfortable to move. The headache now came on at any time of day or night, and sometimes awakened her. It was relieved in half an hour by taking aspirin. Since the exacerbation of the headache she had been subject to nausea and vomiting every morning. The headache and vomiting were quite distinct from each other. She had some dyspepsia and her appetite was poor. Since her illness had commenced she had lost 28 lb. in weight. Since December 1946 she had had amenorrhœa—a pregnancy test three weeks before admission had been negative.

State on examination.—She looked thin and sallow, but her mucous membranes were of good colour. Her weight was 7 st. 12 lb. Both optic discs were somewhat pale with indistinct edges. There was no definite swelling, and the vessels were normal. She had slight weakness of both external recti. Otherwise the rest of her nervous system was normal. Apart from a right nephrectomy scar, there were no other abnormal clinical findings.

Clinical course.—During the first week of admission her temperature rose to 99·2° F. at times and her pulse varied from 80 to 100 per minute. She continued to have early morning headache and vomiting and her temperature occasionally rose to 101° F.

On May 5 she had a ventriculography, which was normal, apart from a rise in

ventricular pressure being recorded. The next day she was euphoric and mentally confused. Also she was dyspraxic and aphasic. After the ventricular pressure was lowered by a ventricular tap she became mentally normal, although her plantars were now indefinite, the left one being probably extensor. She also showed papilloedema, more marked in the right eye.

As her cerebrospinal fluid had shown a pleocytosis (*see* Table III) she was given anti-syphilitic treatment, although her blood and cerebrospinal fluid Wassermann reactions were negative. She was given intramuscular penicillin 225,000 units daily, and also treated with mercury and iodides by mouth. In spite of this her condition began to deteriorate and the pyrexia continued unchanged. She was drowsy and confused and had lost a further 11 lb. in weight. She was then started on intravenous injections of neoarsphenamine.

On June 9 a small hæmorrhage was present on the right optic disc. Her general condition was unchanged although at about this time she became apyrexial for a week. Ventriculography was repeated with the same findings as previously. She then became apyrexial and her condition improved. She became free of headaches and vomiting and her pulse-rate became normal.

Five months after her admission she was discharged, and requested to return in two months' time for review.

In October she was readmitted. She still had a pyrexia rising to 100° F. Her plantar reflexes were variable, sometimes being flexor and sometimes extensor. Two weeks after she was readmitted her temperature became normal for a week and then the pyrexia recommenced, not rising above 100·4° F. Her pulse-rate was increased to 120. Her headache and vomiting returned and she again became confused and euphoric. Her memory for recent events was deteriorating. Both optic discs became blurred on the nasal margins. Her weight was still increasing and amenorrhœa was still present. In November she developed slight ptosis, nystagmus on deviation of her eyes to the right, and lost her abdominal reflexes. Lumbar puncture showed an increase of the initial pressure to 270 and a free rise and fall was not obtained. During the next six weeks her symptoms increased in intensity. She developed giddiness and attacks of loss of vision. The giddiness was aggravated by moving the head. There was nystagmus on looking to the right and left, and vertical nystagmus on looking upwards. The swelling of her optic discs had increased. She commenced to have diplopia. She became drowsy. Her gait was swaying and unsteady. An otological examination was carried out in January 1948 by Dr. C. S. Hallpike who reported as follows: Cochlear function normal. Vestibular function: first degree slight spontaneous nystagmus to the left and upwards. Optokinetic nystagmus, slight directional preponderance to the left, directional preponderance upwards. Positional nystagmus; with the head back and to the right, transient vertigo and second-degree nystagmus to the left; with the head back and to the left, slighter vertigo and second-degree nystagmus to the right. Caloric tests normal. These findings indicated a deep-seated mid-line lesion of the cerebellum.

Ventriculography on January 3 showed a slight symmetrical hydrocephalus. The ventricular system was completely outlined and there was no evidence of any destruction of this system.

On January 19 a suboccipital decompression was performed by Mr. Wylie McKissock, whose operation findings were as follows: "The dura was under tension. The cerebellar convolutions were found to lie with their lower poles exactly at the level of the lower border of the foramen magnum. The arachnoid of the posterior wall of the cisterna magna was rather whitish in colour. A portion was removed for section. The cerebellar convolutions were firmly stuck together in the mid-line, and could not be separated by blunt dissection. It was necessary to use the hook and diathermy to separate them. The posterior inferior cerebellar arteries were firmly

adherent to the tonsils. The tonsils were eventually separated and an opening was made into the 4th ventricle and a gush of cerebrospinal fluid obtained. The 4th ventricle foramina were partly if not completely obstructed by adhesions. The final opening into the 4th ventricle measured half an inch in length. The condition found was an arachnoiditis with tonsillar and 4th ventricle adhesions."

Histological report.—Dr. J. G. Greenfield reported on the removed tissue as follows: "Microscopically the arachnoid shows fibrous thickening. There is a well-marked cellular infiltration consisting predominantly of lymphocytes and large mononuclear cells, with very occasional polymorphonuclear leucocytes and plasma cells. In several places there are definite follicular arrangements of endothelioid cells surrounded by lymphocytes. One such follicle has a peripheral giant cell with

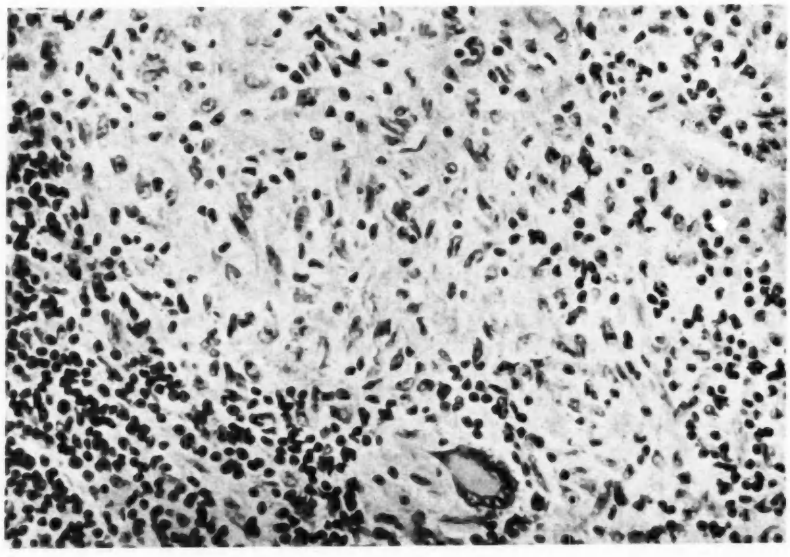


FIG. 1 (*Case* 1)

Section of lymph node × 300. Hæmatoxylin and eosin. Shows a collection of cells of the endothelioid type. To the left of the figure are seen part of the surrounding zone of lymphocytes. In the lower part is seen a giant cell.

its numerous nuclei scattered throughout its cytoplasm. These follicles do not show central necrosis, nor can acid-alcohol fast bacilli be seen in the sections. The capillaries appear healthy. The appearances are strongly suggestive of a tuberculous infection though the possibility of some other chronic granulomatous condition such as meningovascular syphilis must be considered" (*see* fig. 1).

After the operation the patient's condition improved and she became much brighter. She remained practically free from pyrexia. Apart from a transient 6th nerve palsy in early February she continued to improve and became free of symptoms. She was discharged in March 1948.

In April she was seen again as an outpatient. She stated that she was very well although on one or two occasions she had vomited. She was quite free of headache. She now weighed over 10 st. Amenorrhœa was still present. Both optic discs looked somewhat pale. The lower abdominal reflexes were still absent.

Special investigations.—During her illness the following investigations had been performed:

Mantoux test: This was negative to 1 : 10,000, 1 : 1,000, and 1 : 100, on two occasions.

The cerebrospinal fluid was repeatedly examined for organisms, including tubercle bacilli and torula, with negative results. Cultures were always sterile.

Blood-count.—This showed a polymorphonuclear leucocytosis. Leucocytes, 13,200 per c.mm., polymorphonuclear leucocytes 79 per cent., lymphocytes 21 per cent. (4.11.47).

Sedimentation rate (modified Westergren, 100 mm.): 14.4.47; 5 mm. first hour, 13 mm. two hours. 8.7.47: 2 mm. first hour, 4 mm. two hours. 11.11.47: 5 mm. first hour, 11 mm. two hours.

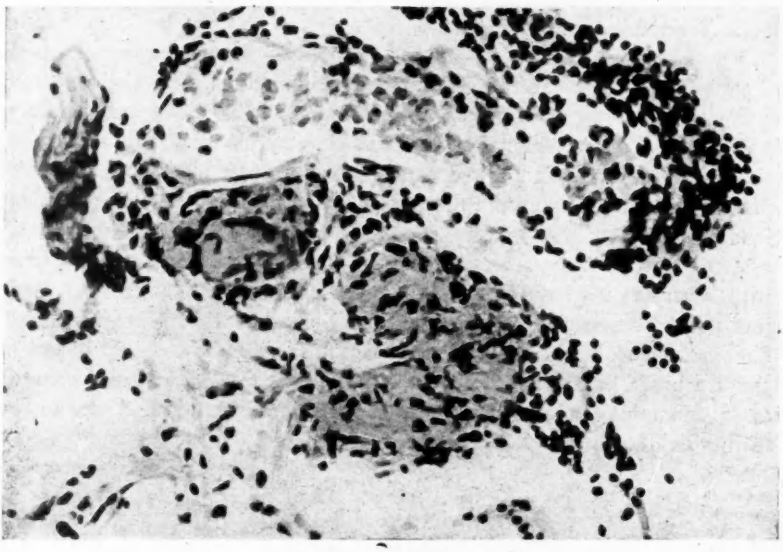


FIG. 2 (*Case* 3)

Part of section of arachnoid × 300. Hæmatoxylin and Van Gieson's stain. Shows a multinucleated giant cell and a collection of endothelioid cells lying outside the wall of a small blood-vessel. In the upper part of the picture is a collection of lymphocytes.

Plasma proteins (February 1948): Total protein 6·9 grammes, albumen 4·25 grammes per cent., globulin 2·65 grammes per cent.

Radiological investigation of her skull, paranasal sinuses, hands, limb muscles, and chest showed no abnormality. Her renal tract showed no evidence of calculi.

Blood culture was sterile and there was no agglutination of *B. typhosus, B. paratyphosus* A or B, or of *Br. abortus.*

The urine showed a trace of albumen and a few leucocytes and red cells on one occasion. Culture was always sterile. No ova or parasites were present in the fæces and no pathogenic organisms could be grown from them.

E.E.G. (15.5.47, Dr. Denis Hill): "Diffuse asymmetrical abnormalities were present. An excess of fast activity of high voltage was seen in the right central

area and irregular delta rhythm at 3 cycles per second in the right temporal and post-central areas. Diffuse theta rhythm at 5 cycles per second was present on the left side. There was no focal abnormality. It suggested an acquired lesion but there was no evidence for a cortical one. Query deep right post-central."

E.E.G. repeated later (13.11.47, Dr. Denis Williams): The E.E.G. recorded from 14 standard positions was abnormal. There was a dominant frequency of 11-per second with abnormal 5 a second cycles in both parietal regions. The abnormality in the right mid-temporal region which was previously described was still present. It was more evident behind than in front of the ear. The changes still looked like those of an organic lesion.

Summary

A woman aged 23 had headache and vomiting and mild irregular fever for almost two years. In the early part of her illness there was a mild remission which lasted about three months. Her symptoms then became more severe and she had amenorrhœa. She became dull and sleepy and her weight began to increase. She developed bilateral papilloedema and positional nystagmus. Her cerebrospinal fluid was persistently abnormal. It showed a raised protein and pleocytosis with the presence at times of polymorphonuclear leucocytes and large mononuclear leucocytes. Ventriculography showed dilatation of all the ventricular system. A posterior fossa exploration revealed adhesive arachnoiditis with obstruction of the 4th ventricle foramina. An opening was made into the 4th ventricle allowing the free circulation of cerebrospinal fluid. She made a slow but steady recovery. A biopsy showed infiltration of the arachnoid with endothelioid cells, multinuclear giant cells, lymphocytes, mononuclear, leucocytes, and plasma cells, with a tendency to the formation of follicles.

Discussion

The localization of the lesion in this patient presented considerable difficulty and was indicated clinically as being in the region of the cerebellum by the results of the otological examination. The diagnosis of the pathology lay between three conditions: syphilis, tuberculosis, and sarcoidosis. There was no evidence that this patient had syphilis. She had a negative Wassermann reaction in her blood and cerebrospinal fluid. She did not respond in any way to antisyphilitic treatment. It is difficult to believe that she was suffering from a simple tuberculous meningitis or arachnoiditis. There is no evidence of tuberculosis elsewhere, and she seems to have made a good recovery after a very prolonged illness. She has been putting on weight and her sedimentation rate has only been slightly elevated, and at times has been normal even when she has been quite ill. No tubercle bacilli have ever been found and her Mantoux reaction has been negative to 1: 100. It would therefore seem unlikely that the condition was a simple tuberculous infection. Although not

absolutely conclusive, there does seem to be much positive evidence in favour of the diagnosis of sarcoidosis. This case from the clinical aspect, the operative findings, and also the histological findings, bears a very great resemblance to the case of sarcoidosis described by Erickson, Odom, and Stern. Both patients undoubtedly had a meningo-encephalitis associated with an adhesive arachnoiditis of the posterior fossa, with occlusion of the 4th ventricle foramina, and histologically both cases have shown infiltration of the arachnoid with endothelioid cells, giant cells, lymphocytes (round cells), plasma cells and mononuclear leucocytes. The cerebrospinal fluid in both cases showed an increase in protein and a pleocytosis. The prolonged low-grade fever which this patient showed is also consistent with this view.

Lesions of the Brain and Spinal Cord

Apart from the changes secondary to the infiltration of the leptomeninges, the brain and spinal cord may be directly infiltrated by sarcoid tissue, or may show perivascular changes as already described.

Roos (1937) reported a child aged 6 who had a prolonged low-grade pyrexia over a period of eighteen months. During this time she had a skin eruption typical of the condition, and developed lymphadenitis, an enlarged liver and spleen, and uveitis. Fourteen months after the onset of the illness she developed papillœdema and very soon afterwards became mentally confused and had focal convulsions involving the left arm. Four months later she had convulsions in which the right side of the body was mainly involved. The cerebrospinal fluid pressure was raised, and the fluid showed a pleocytosis. There could be little doubt that she had scattered lesions involving both cerebral hemispheres.

Focal convulsions were also reported by Lindau and Löwegren (1940). Their patient had marked neck rigidity and was stuporose. There was a disturbance of speech which was probably a dysphasia, as the focal convulsions affected the right arm.

Lenartowicz and Rothfeld (1930), Reis and Rothfeld (1931) reported a girl aged 17 who showed very gross involvement of her nervous system. She complained of headaches and six months later her left eye was completely blind and she was only able to count fingers with the right eye. The left optic disc showed 20 dioptres of swelling and the right optic disc 5 dioptres of swelling with some atrophy. Bilateral exopthalmos was present. The pupils reacted poorly to light. The right lower face and right leg were weak and bilateral extensor plantar responses were present. There was an extensive eruption involving the face, trunk and limbs, which had preceded the onset of neurological symptoms. Her fingers were swollen. Radiologically her skull showed an enlarged sella

turcica and there was evidence of raised intracranial pressure. She became apathetic, drowsy and incontinent, developed epileptiform seizures, and two years after the onset of her neurological symptoms she died.

There is a very full account of the post-mortem findings. There was infiltration of the infundibulum, optic chiasma, optic nerves, right olfractory bulb and right gyrus rectus. The left temporal lobe was almost filled with infiltrate, and the left corpus striatum and right caudate nucleus were also infiltrated. The subthalamic region and base of the 3rd ventricle were involved by infiltrate. There were two nodules in the cerebellum. Both lateral ventricles were widened, the left was larger than the right. Microscopically, around the small blood-vessels there were epithelioid cells and lymphocytic infiltration. In the brain tissue were aggregations of cells, either epithelioid cells or epithelioid cells mixed with plasma cells. The borders of these lesions were formed of lymphocytes. Often these lesions were surrounded by connective tissue or thickened glia. In some places adjacent to aggregations of lesions there was encephalomalacia. In the nervous system no caseation or giant cells were present. The cerebrospinal fluid contained an increased globulin.

Rothfell (1930) recorded a male aged 30 with lupus pernio who complained of attacks of unconsciousness with convulsions. He had headache, vomiting and giddiness. His gait was unsteady, his speech was confused. On examination he showed nystagmus, weakness of the masseters, and right facial weakness. The soft palate was paralysed and there was weakness and fibrillation of the tongue. He had cerebellar signs in his right arm, increased deep reflexes on the right side with diminished abdominal reflexes on the same side. He had a cerebellar gait and deviated to the right when walking. He then developed a bilateral ptosis and almost complete external ophthalmoplegia. Three years later he had a spastic paralysis with cerebellar signs.

A case that showed an extrapyramidal syndrome in the form of generalized choreiform movements was reported by Ernsting and Sillevis Smitt (1944, Case 4).

There are a small number of cases recorded in which the main neurological features of the disease were in the brain-stem or the spinal cord.

Uehlinger (1942) described a fatal case with a mid-brain syndrome.

Zollinger and Meyerburg (1942) described the post-mortem findings of a case that during life was regarded as suffering from disseminated sclerosis. In the brain, especially the brain-stem, there was a granulomatous condition of the Virchow-Robin spaces that had the typical histological features.

Mohn (1933) described a patient, a woman aged 28, whose illness

commenced with pyrexia followed by a bilateral facial paralysis of the peripheral type, and loss of taste on the anterior two-thirds of the tongue. Her soft palate was paralysed. Three weeks later she developed a bilateral parotitis, lymphadenitis and enlargement of the submaxillary and lachrymal glands. There was early papillœdema. Her cerebrospinal fluid showed a slight pleocytosis. Five weeks after the onset of her facial paralysis she developed deafness, her arms became weak and hypotonic and they showed cerebellar signs. She had a spastic paralysis of her legs. The deep reflexes in her arms became weak and her plantar reflexes extensor. She also showed Rombergism. A bilateral uveitis was present.

Her symptoms improved but nine months after the onset she still showed facial paralysis.

In the patient described by Levin (1935) there was sensory loss on the centre of the face with an inconstant extensor plantar response.

Folger (1936) described a case in which there was loss of sensation from the neck to the waist. This sensory disturbance cleared up after a week.

Reisner (1944) reported a case in which the findings pointed to a lesion in the sacral segments of the spinal cord.

Two cases in whom vascular catastrophes occurred were described by Nickerson (1937). One died after a cerebellar hæmorrhage, and the other died as a result of the rupture of an aneurysm on the middle cerebral artery. The vascular changes were considered to be unrelated to sarcoidosis.

Treatment

Curtis, Taylor and Grekin (1947) have reported on the use of calciferol and dihydrotachysterol. The use of calciferol was associated with severe reactions in a patient who had lesions of his central nervous system.

Snider (1948) has used nitrogen mustard.

Summary and Conclusions

A review has been made from the literature of 115 cases of sarcoidosis in which the nervous system has been involved, and a further three cases are reported in detail. Two of these had a polyneuritis involving the cranial and peripheral nerves, and the third had an adhesive arachnoiditis of the posterior fossa.

The disease may involve any part of the nervous system. The structures that are particularly likely to be affected are the optic nerves and retina, the facial, glossopharyngeal and vagus nerves, the pars intermedia of the pituitary gland and pituitary stalk, and the peripheral nerves.

The central nervous system may develop a meningo-encephalitis or

meningo-myelitis, may exhibit localized infiltration by sarcoid tissue, or may be affected by tumour-like masses in the dura mater. There may also be hydrocephalus and adhesive arachnoiditis. Clinically, these conditions may manifest themselves by causing focal or generalized disturbances of cerebral function.

Changes in the cerebrospinal fluid may be present, the commonest abnormal findings being a pleocytosis, an increase in globulin, and an increase in protein.

The diagnosis of sarcoidosis should always receive serious consideration in any case of nervous disease of obscure ætiology.

I wish to express my thanks to Sir Charles Symonds, Dr. J. Purdon Martin, Dr. Macdonald Critchley, and Mr. Wylie McKissock for permission to publish cases under their care, and to the other members of the staff of the National Hospital whose findings I have used.

I would like to thank Dr. J. G. Greenfield for much assistance and helpful advice.

TABLE I.—POLYNEURITIS SARCOIDOSIS

Author	*Sensory changes*	*Motor Changes*	*Reflexes*
Boeck	Anæsthesia in area supplied by left ulnar nerve		
Critchley and Phillips	Absent vibration sensibility over ankles	Ptosis. Atrophy of small hand muscles: movements of hands, elbows and legs feeble.	All tendon reflexes present
Ernsting and Sillevis Smitt Case 5	Hyperæsthesia for pain and temperature. Muscles and nerve trunks tender	Limbs atrophied	Deep reflexes diminished or absent
Feiling and Viner	Numbness and tingling of hands	Bilateral facial weakness. Fine movements of fingers unsteady	Supinator, triceps, knee and ankle-jerks absent
Garland and Thomson (1933)	Paræsthesiæ feet, calves tender. Sensory ataxia	Ptosis, aphonia. Arms hypotonic, legs hypotonic and weak, bilateral footdrop	Right epigastric sluggish, lower abdominals absent. Brisk tendon reflexes
Garland and Thomson (1934)	Deafness, hypalgesia glove and stocking distribution. Vibration diminished over ankles. Sensory ataxia	Right 7th paresis. Flaccid paralysis arms, weak legs	Absent deep reflexes

TABLE I.—POLYNEURITIS SARCOIDOSIS—*continued*

Author	*Sensory changes*	*Motor Changes*	*Reflexes*
Heerfordt	Hypæsthesia, anæsthesia ulnar borders of both hands, 2nd and 3rd fingers of right hand. Hypalgesia and hypæsthesia left abdomen	Right facial paresis nasal speech, dysphagia	Left epigastric reflex absent. Tendon reflexes increased
Colover 1	Hypalgesia below right elbow and below both knees	Legs weak	Right knee-jerk and right triceps-jerk absent
Colover 2	Cold patches on leg, trunk and mastoid region	Right deltoid and right triceps wasted	Knee-jerks sluggish, ankle-jerks absent
Kuhlefelt	Sensation blunted slightly in places		Left knee-jerk sluggish
Mazza	Loss of pain and touch forearm and hand; temperature and pressure affected to a slighter degree	Weakness of forearm and hand	
MacBride	Light touch diminished 2nd and 3rd divisions left trigeminal area. Paræsthesiæ left hand; pain from shoulder to tip of left forefinger, numbness of tips of middle three fingers	Bilateral facial paralysis, dysphagia, weakness of legs	
MacCulloch		Bilateral facial weakness	Unequal knee-jerks
Ottonello and Anardi	Taste disturbance, paræsthesiæ of limbs, vibration sensibility diminished. Tender nerve trunks	Motor 5th, 7th, 9th and 10th cranial nerves impaired. Limbs hypotonic	Right triceps, both knee and both ankle jerks absent
Revilliod		Bilateral 6th, left 7th bilateral 9th, 10th, 11th, and right 12th cranial nerves paralysed. All four limbs paralysed	Absent knee-jerks
Rogers and Bodman	Sensory symptoms right arm, left 4th finger, right gluteal region, right leg, right sole, and left foot	Wrist drop; flaccid paralysis of both lower limbs, foot drop. Jerky movements of limbs and trunk	Epigastric reflexes absent. Left triceps and knee-jerks absent. Plantars absent
Tepper		Bilateral facial paralysis	Deep reflexes absent

TABLE I.—POLYNEURITIS SARCOIDOSIS—*continued*

Author	*Sensory changes*	*Motor changes*	*Reflexes*
Thompson, Case 3	Numbness of face and neck	Bilateral facial weakness	Corneal reflexes, knee and ankle jerks absent
Thompson, Case 5	Anosmia	Facial paralysis soft palate and right vocal cord weak	Hypoactive tendon reflexes
Viets	Legs numb, loss of deep muscle sense of toes and feet	Bilateral facial paralysis. Weakness of arms and legs. Loss of sphincter control	Deep reflexes absent
Waldenström	Girdle pains in region of costal arch	Right facial paralysis	Loss of deep reflexes in lower limbs

TABLE II.—ABNORMAL C.S.F. FINDINGS IN CASES OF SARCOIDOSIS

Author	*Pressure mm. aq.*	*Protein mg. per cent.*	*Nonne*	*Pandy*	*Cells per cmm.*	*Cell types present*	*Other observations*
Coleman and Meredith	275				3	L 2 P 1	
Erickson, Odom and Stern	370	261			50	L	
Ernsting and Smitt							
Case 1					15		
Case 2			±	+			
Case 5	300	720	+++	+++	52	P & L	Lange 1111123443 Xanthochromia
Feiling and Viner		15			15	L	
Lesné, Launay and Sée		220					
Levin		90		±	12	L 11 P 1	
MacBride			Haze		8	LM 5%	
Naumann	420			+	12	L+	
Ottonello and Anardi	200	300	−	+	15		Benzoin 0000022200000000
Rogers and Bodman		100	±	+			Lange 0000001221
Reis and Rothfeld			++++	++++			
Roos	240		++	++	8·9	4·6 L	
Tepper		120	++		68	L 96% P 4%	Lange 1112344321
Thompson			+	+	15	L	Mastic 5554320000
Viets		348					Lange 2222333100

Key: L = lymphocytes; P = polymorphonuclear leucocytes; L M = large mononuclears
Unless otherwise stated cells present are lymphocytes.

TABLE III.—CEREBROSPINAL FLUID, CASE 3

Date	Pressure mm. aq.	Protein mg. per cent.	Nonne Apelt	Pandy	Cells per c.mm.	Cells type	Other observations
2.4.47 ..	190	140	+	+	162	L 136 P 18 LM 8	Lange 0123321100
13.5.47	130	160		++	67	L 95% P 3% LM 2%	Sugar 0·017 gramme per cent.
4.6.47 ..	150	170	+	+	60	L 48 LM 8 P 2	Lange 0121100000
7.7.47 ..	150	200	+	+	35	L 31 LM 2 P 2	Lange 0011221100 Faint straw colour
17.7.47 ..		100	+	+	26	L	
19.7.47 ..		150	±	+	13	L	
30.7.47 ..		50	—	+	32	L	Lange 1122111000 Sugar 0·036 gramme per cent.
8.8.47 ..	130	90	±	±	22	L. 20 P 2	Lange 1112210000 Sugar 0·040 gramme per cent.
11.10.47 ..	200	220	+	+	14	L 85 P 15	Lange 00011100000
13.11.47 ..	270	120	+	+	22	L	Chlorides 0·680 gramme per cent. Sugar 0·038 gramme per cent.
1.12.47 ..	250	130	+	++	30	L	Lange 0011210000 Chlorides 0·690 gramme per cent. Sugar 0·034 gramme per cent.
12.1.48 ..	220	160	+	+	12	L	Coagulum Lange 0112333100
19.1.48 ..							Operation
18.2.48 ..	210	120		+	10	L	Small coagulum Lange 0012221000 Chlorides 0·720 gramme per cent.

Key: L = lymphocytes; P = polymorphonuclear leucocytes; L M = large mononuclears.

REFERENCES

BAHR, G. von (1938) *Acta Ophth.*, **16**, 101.

BERNSTEIN, M., KONZLEMAN, F. W., and SIDLICK, D. M. (1929) *Arch. Int. Med.*, **44**, 721.

BOECK, C. (1916) *Arch. Derm. Syph. Wien.*, **121**, 707.

CAMERON, C., and DAWSON, E. K. (1942) *Edinb. Med. J.*, **49**, 737.

COGAN, D. (1935) *Amer. J. Ophthal.*, **18**, 637.

COHEN, S. J., and RABINOWITZ, M. A. (1935) *J. Amer. Med. Ass.*, **105**, 496.

COLEMAN, C. C., and MEREDITH, J. M. (1940) *Arch. Neurol. Psychiat. Chicago*, **44**, 1076.

CRITCHLEY, M., and PHILLIPS, P. (1924) *Lancet*, **2**, 906.
CURTIS, A. C., TAYLOR H., and GREKIN, R. H. (1947) *J. Invest. Dermat.*, **9**, 131.
DAVIES, T. A. L. (1934) *Lancet*, **2**, 746.
DOPTER (1904) *Gaz. Hop. Paris*, **77**, 857.
DOR, H. (1900) Quotation, *Lancet*, 1516.
DOUB, H. P., and MENAGH, F. R. (1929) *Amer. J. Roentgen.*, **21**, 149.
ERNSTING, W., and SILLEVIS SMITT, W. G. (1944) *Geneesk. Bl.*, **41**, 1.
ELSHOUT, N. (1942) *Ned. Tijdschr. Geneesk.*, **86**, 1474.
ERICKSON, T. C., ODOM, G. L., and STERN, K. (1942) *Arch. Neurol. Psychiat. Chicago*, **48**, 613.
FEILING, A. (1914) *Quart. J. Med.*, **8**, 255.
—— and VINER, G. (1921) *J. Neurol. Psychopath.*, **2**, 353.
FORD, F. R. (1945) Diseases of the Nervous System, in Infancy, Childhood and Adolescence. Springfield, Illinois (Charles C. Thomas), P. 545.
FLANDIN, C., PARAT, M., and POUMEAU-DELILLE, G. (1936) *Bull. Soc. med. Hop. Paris*, **52**, 1423.
FOLGER, H. P. (1936) *Arch. Ophthal. N.Y.*, **15**, 1098.
FRANCESCHETTI, A., and DE MORSIER, G. (1941) *Rev. med. Suisse rom.*, **61**, 129.
FREUDENTHAL, W. (1948) *Brit. J. Tuberc.*, **42**, 11.
GARLAND, H. G., and THOMSON, J. G. (1933) *Quart. J. Med.*, **2**, 157.
——, —— (1934) *Lancet*, **2**, 743.
GJESSING, H. G. A. (1916) *Klin. Mbl. Augenheilk.*, **56**, 252.
GRAVESEN, P. B. (1943) *Zbl. ges. TuberkForsch.*, **55**, 489.
GUILLAIN, G. (1922) *Bull. Acad. Méd. Paris*, **88**, 80.
HAAS, G., and JOSEPH, H. (1908) *Ann. Oculist. Paris*, **139**, 130.
HAMBURGER, L. P., and SCHAFFER, A. J. (1928) *Amer. J. Dis. Child.*, **36**, 434.
HANTSCHMANN, L. (1939) *Ergeb. ges. TuberkForsch.*, **9**, 1.
HARRELL, G. T. (1940) *Arch Intern. Med.*, **65**, 1003.
HEERFORDT, C. F. (1909) *v. Graefes Arch. Ophthal.*, **70**, 254.
HOYLE, C. (1947) *Brit. J. Tuberc.*, **41**, 92.
JERSILD, M. (1939) *Ann. Derm. Syph. Paris*, **10**, 641.
KUHLEFELT, E. (1917) *Brit. J. Ophthal.*, **1**, 621.
LEEKSMA, H. W. (1916) *Ned. Tijdschr. Geneesk*, **2**, 1126.
LEMMING, R. (1940) *Acta med. Scand.*, **103**, 400.
LENARTOWICZ, J., and ROTHFELD, J. (1930) *Arch. Derm. Syph. Wien.*, **161**, 504.
LESNE, F., COUTELA, C., and LEVESQUE, J. (1938) *Bull. Soc. med. Hop. Paris*, **54**, 9.
LESNÉ, E., LOUNAY, C., and SEÉ, G. (1935) *Bull. Soc. med. Hop. Paris*, **51**, 1137.
LEVIN, P. M. (1935) *J. Nerv. ment. Dis.*, **81**, 176.
LIEGEOIS (1891) *Prog. Med. Paris*, **2**, 241.
LINDAU, A., and LÖWEGREN, A. (1940) *Acta med. Scand.*, **105**, 242.
LONGCOPE, W. T., and PIERSON, J. W. (1937) *Johns Hopk. Hosp. Bull.*, **60**, 223.
—— (1941) *J. Amer. Med. Ass.*, **117**, 1321.
MACBRIDE, H. J. (1923) *J. Neurol. Psychopath.*, **4**, 242.
MCCULLOCH, J. D. (1927) *Trans. Ophthal. Soc. U.K.*, **47**, 410.
MACKAY, G. (1917) *Brit. J. Ophthal.*, **1**, 612.
—— (1921) *Trans. Ophthal. Soc. U.K.*, **41**, 209.
MCMURRY, A. L. (1934) *Trans. Ophthal. Soc. U.K.*, **54**, 561.
MAZZA, G. (1908) *Arch. Derm. Syph. Wien.*, **91**, 57.
MEISSNER, M. (1938) *Klin. Mbl. Augenheilk*, **100**, 124.
MERRILL, H. G., and OAKS, L. W. (1931) *Amer. J. Ophthal.*, **14**, 15.
MEYER, F. W. (1938) *Klin. Mbl. Augenheilk*, **100**, 377.
MICHELSON, H. E. (1948) *J. Amer. Med. Ass.*, **136**, 1034.
MOHN, A. (1933) *Acta Ophthal. KBN.*, **11**, 397.
—— (1934) *Amer. J. Ophthal.*, **17**, 183.

MUCHA, V., and ORCHECHOWSKI, K. (1919) *Wien. Klin. Wschr.*, **32**, 25.
NAUMANN, O. (1938) *Z. Kinderheilk.*, **60**, 1.
NICKERSON, D. A. (1937) *Arch. Path. Lab. Med.*, **24**, 19.
OTTONELLO, P., and ANARDI, T. (1940) *Riv. Patol. Nerv. Ment.*, **56**, Fasc. 2, 185.
PALMER, J. H. (1940) *Canad. med. Ass. J.*, **43**, 11.
PARKER, G. (1926) *Bristol med.-chir. J.*, **43**, 73.
PAUTRIER, L. M. (1937) *Bull. Soc. Med. Hop. Paris*, **54**, 1608.
—— (1938*a*) *Ann. Derm. Syph. Paris*, **9**, 161.
—— (1938*b*) *Pr. Med.*, **46**, 1, 518.
—— (1939) *Ann. Derm. Syph.*, **10**, 97.
—— (1940) Maladie de Besnier-Boeck-Schaumann, Paris (Masson et Cie).
—— (1948) *Brit. J. Tuberc.*, **42**, 1.
PINNER, M. (1938) *Amer. Rev. Tuberc.*, **37**, 690.
RAMSAY, A. M. (1921) *Trans. Ophthal. Soc. U.K.*, **41**, 194.
REISNER, D. (1944) *Amer. Rev. Tuberc.*, **49**, 289.
REVILLIOD, L. (1896) *Rev. med. Suisse rom.*, 752.
REIS, W., and ROTHFELD, J. (1931) *v. Graefes Arch. Ophthal.*, **126**, 357.
RIETH, H. (1919) *Klin. Mbl. Augenheilk.*, **63**, 527.
ROGERS, B., and BODMAN, J. H. (1926) *Bristol med.-chir. J.*, **43**, 84.
ROOS, B. (1937) *Z. Kinderheilk.*, **59**, 280.
—— (1938) *Acta Psychiat. Kbh.*, **13**, 40.
ROTHFELD, J. (1930) *Klin. Wschr.*, **9**, 1, 1030.
SALVESEN, H. A. (1935) *Acta med. Scand.*, **86**, 127.
SAVIN, L. H. (1934) *Trans. Ophthal. Soc. U.K.*, **54**, 549.
SCHAUMANN, J. (1941) *Acta med. Scand.*, **106**, 239.
—— (1936) *Brit. J. Derm.*, **48**, 399.
SCHÜPBACH, A. (1936) *Schweiz. med. Wschr.*, **17**, 1182.
SCOTT, R. B. (1938) *Brit. med. J.*, **2**, 777.
SICARD, (1914) *Rev. Neurol.*, **27**, 706.
SIMONS, A., and MERKEL, H. (1917) *Neurol. Zbl.*, **36**, 258.
SNAPPER, I., and POMPEN, A. W. (1938) Pseudo-tuberculosis in Man. Haarlem (De Erven F. Bohn, N.V.).
SNIDER, G. E. (1948) *Sth. Med. J. Birmingham, Ala.*, **41**, 11.
SOUTER, W. C. (1929) *Trans. Ophthal. Soc. U.K.*, **49**, 113.
STRASMAN (1911) *Mitt. Grenzgeb. Med. Chir.*, **23**, 351.
SUNDELIN, F. (1925) *Acta med. Scand.*, **62**, 442.
TAIT, C. B. V. (1934) *Lancet*, **2**, 748.
TANNER, S. E., and MCMURRY, A. L. (1934) *Brit. med. J.*, **2**, 1041.
TEPPER, R. (1947) *Brit. med. J.*, **2**, 1034.
TILLGREN, J. (1935) *Brit. J. Derm.*, **47**, 223.
THOMPSON, W. C. (1937) *Arch. int. Med.*, **59**, 646.
TOULANT, P., and MORARD, G. (1936) *Arch. Ophtal. Paris*, **53**, 321.
UEHLINGER (1942) *Schweiz. Med. Wschr.*, **23**, 826.
URBAN, O. (1910) *Arch. Derm. Syph. Wien.*, **101**, 175.
UTHOFF, W. (1912) *Klin. Mbl. Augenheilk*, **50**, 1, 474.
VIETS, H. R. (1927) *Arch. Neurol. Psychiat. Chicago.*, **17**, 794.
WALDERSTRÖM, J. (1937) *Acta med. Scand.*, **91**, 53.
WINKLER, M. (1905) *Arch. Derm. Syph. Wien.*, **77**, 3.
ZOLLINGER, and MEYERBURG, V. (1942) *Schweiz. med. Wschr.*, **23**, 825.

Notices of Recent Publications.

Neuroanatomy. By F. A. Mettler. Second Edition. 1948. London: Henry-Kimpton. Price 50s.

This beautifully illustrated text is at its best when the author confines himself to anatomical description, and weakest where he embarks upon physiological considerations.

It was a good tradition in the textbooks of anatomy of years gone by that restricted them to the subject indicated by their title; that is, the subject upon which the author had the authority conferred upon him by training and experience. Anatomy has suffered by the modern departure from this tradition and physiology has not gained.

Thus the reader will derive the most complete and reliable information from the chapters in Mettler's book that deal with morphology; that is, the chapters on the brain-stem and the thalamus. For his reflex physiology, he will be well advised to go to Sherrington's "Integrative Action," and for his account of the frontal cortex, both cytoarchitectonic and physiological to Lashley and Clark and to such sources as are not based upon the doubtful parcellations of the Vogts.

If the reader will bear these qualifications in his mind he will find the purely morphological accounts of the nervous system from the thalamus caudalwards of great value and the illustrations of gross and miscroscopic anatomy unequalled.

Minor criticisms are that fig. 138, purporting to derive from Merritt, Mettler and Putnam's "Fundamentals of Neurology" is an unacknowledged redrawing of a figure from a paper by Woollard, Weddall and Harpman in the *Journal of Anatomy*, 1940, **74**, 427. While the term "neural hookup" can scarcely be regarded as a euphonious or scientific improvement upon "synapse."

Clinical Psychology. A Case Book of the Neuroses and their Treatment. By Charles Berg. 1948. London: George Allen and Unwin Ltd. Pp. 503. Price £1 5s.

The main theme of this book is introduced by a personal Odyssey and by a discussion of the biological basis of the ætiology of nervous disorders, in which hereditary factors receive some appraisement. We are then led to consider clinical syndromes, anxiety, hysteria, epilepsy, depression, &c., in the framework of a psychoanalytic interpretation, and with detailed illustrations from the analysis of particular patients. The author has the gift of writing lucidly and in an engaging style, and throughout the book evidence is shown of clinical insight and judgment. The most important part of the work is, however, the handling of theory, and this shows a grave lack of self-criticism. The effort is, for instance, made to bring psychoanalytic theory in line with biology; but a Lamarckianism is preferred, which finds almost no acceptance among modern biologists.

A complete chapter is devoted to the psychopathology of schizophrenia. Physical theories of ætiology are mentioned only to be dismissed. The profound studies of Jaspers and his followers which, on the basis of a refined analysis of clinical data,

have shown which of the symptoms of the schizophrenic are accountable as psychological reactions, and which are to be attributed to the specific processes of the disease, are apparently unknown to the author. The hypothesis is advanced that the morbid process is one of sexual frustration and conflict, leading to an endeavour by the subject to avoid pain or achieve gratification through a method of self-injected euphoria. This morbid reaction tendency can accumulate through the generations by a process of Lamarckian-like inheritance. The psychiatrist can only observe that the mental experiences of the schizophrenic bear no resemblance to a self-injected euphoria, and that any psychogenic theory is incapable of explaining the physical changes that occur in schizophrenia, which may be so grave and rapid as to lead from health to death in a few weeks. And the geneticist can only comment that inheritance in schizophrenia shows no evidence of a Lamarckian quality but fits well enough with modern genetical concepts based on Mendelism.

Just as rival theories of ætiology of mental disorders receive severe or disparaging treatment, so also do the rivals of psychoanalysis in the field of therapy. The advent of physical methods of treatment has made a ghastly state of affairs, for which the only remedy would be for an outraged public to arise and perform decapitation, in return for decerebration, upon the Himmlers of their psychiatric Buchenwald. This is not the language of controversy. On the other hand criticisms of psychoanalytic theory are countered by the objection that, in so far as they do not come from the psychoanalysed, they are subjectively determined. Whether this be so or not, they still have to be met.

4TH INTERNATIONAL NEUROLOGICAL CONGRESS, PARIS SEPTEMBER 5 TO 10, 1949

THE 4th International Neurological Congress will be held in Paris from Monday, September 5, till Saturday, September 10, 1949.

Scientific Business will comprise discussions upon four main topics, viz.:

(1) The Thalamus and its Pathology.
(2) Electroencephalography and Electromyography.
(3) Virus Diseases of the Nervous System.
(4) The Surgery of Pain.

The official openers of these four topics have already been nominated by the various National Vice-Presidents. Members of the Congress can participate in the discussion, their remarks being strictly limited to five minutes each.

Short papers on any neurological topic will also be given, and members are invited to submit titles and an abstract of their communication to the Secretary, by February 1, 1949. The length of the communication must not exceed ten minutes. No member may give more than two communications.

Membership and Subscriptions.

It has been decided by the General Committee of the Congress that application for membership and all financial contributions must be made through a National Committee for each country, which will transmit all applications for membership and all subscriptions to the General Committee in Paris.

The British National Committee has been constituted by the Section of Neurology of the Royal Society of Medicine, and is as follows:—

President	...	Dr. Anthony Feiling.
Secretary	...	Dr. Macdonald Critchley.
Treasurer	...	Dr. M. J. McArdle.
Other Members	...	Dr. Douglas McAlpine.
		Dr. W. Ritchie Russell.
		Dr. G. Smythe.
		Sir Charles Symonds.

There are two classes of members: (1) full members, i.e. all medical men or women interested in neurology, and (2) associate members, i.e. non-medical men or women interested in the Congress.

Every member of the Section of Neurology of the Royal Society of Medicine is earnestly invited to contribute the sum of 10s. towards the general expenses of the Congress (whether attending or not). The subscription for full members is £2 10s. 0d. and for associate members £1 5s. 0d.

All cheques should be made payable to and sent to:

Dr. M. J. McArdle,
58a, Wimpole Street,
London, W.1,
before April 1, 1949.

Travelling Arrangements and Accommodation.

Details as to hotel accommodation will be published later. The local committee of the Congress have appointed the American Express Company to be the official travel agents.

Macdonald Critchley,
The National Hospital,
Queen Square,
London, W.C.1.

INDEX
TO
BRAIN:
A JOURNAL OF NEUROLOGY,
FOR
VOL. LXXI, 1948.

AUTHORS.

PAGE

Alajouanine, Th.
Aphasia and Artistic Realisation 229

Barr, Murray L.
Observations on the Foramen of Magendie in a Series of Human Brains 281

Bedford, T. H. B.
The Effect of Intracisternal Injection of Saline Solutions on the Pressure of the Cerebrospinal Fluid of the Dog 403

Bird, A.
The Lipidoses and the Central Nervous System 434

Clark, G.
The Mode of Representation in the Motor Cortex 320

Clark, G., and Ward, J. W.
Responses Elicited from the Cortex of Monkeys by Stimulation Through Fixed Electrodes 332

Critchley, M., and Greenfield, J. G.
Olivo-ponto-cerebellar Atrophy 343

Colover, J.
Sarcoidosis, with Involvement of the Nervous System 451

Cumings, J. N.
The Copper and Iron Content of Brain and Liver in the Normal and in Hepatolenticular Degeneration 410

Denny-Brown, D., and Seyffarth, H.
The Grasp Reflex and the Instinctive Grasping Reaction 109

Feindel, W. H., Sinclair, D. C., and Weddell, G.
Referred Pain and Associated Phenomena 184

Gellhorn, E.
The Influence of Alterations in Posture of the Limbs on Cortically Induced Movements 26

Greenfield, J. G., and Critchley, M.
Olivo-ponto-cerebellar Atrophy 343

Greenfield, J. G., Russell Brain, W., and Russell, D. S.
Subacute Inclusion Encephalitis 365

Harpman, J. A.
Observations on Cutaneous Hyperalgesia 34

Haxton, H. A.
Gustatory Sweating 16

Hill, D., and Roubicek, J.
Electroencephalography with Pharyngeal Electrodes 77

Kendall, D.
Thrombosis of Intracranial Veins 386

PAGE

Kugelberg, E.
Demonstration of A and C Fibre Components in the Babinski Plantar Response and the Pathological Flexion Reflex 304

McLardy, T.
Projection of the Centromedian Nucleus of the Human Thalamus ... 290

Mandelbrote, B. M., Stanier, W. M., Thompson, R. H. S., and Thruston, M. N.
Studies on Copper Metabolism in Demyelinating Diseases of the Central Nervous System 212

Marshall, A. H. E., Russell, D. S., and Smith, F. B.
Microglfomatosis. A Form of Reticulosis Affecting the Brain 1

Pickering, G. W.
Lumbar Puncture Headache 274

Rademaker, G. G. J., and Ter Braak, J. W. G.
On the Central Mechanism of Some Optic Reactions 48

Ray, L. J., and Sunderland, S.
The Intraneural Topography of the Sciatic Nerve and its Popliteal Division in Man 242

Roth, M.
On a Possible Relationship between Hereditary Ataxia and Peroneal Muscular Atrophy: with a Critical Review of the Problems of "Intermediate Forms" in the Degenerative Disorders of the Central Nervous System 416

Roubicek, J., and Hill, D.
Electroencephalography with Pharyngeal Electrodes 77

Russell Brain, W., Greenfield, J. G., and Russell, D. S.
Subacute Inclusion Encephalitis 365

Russell, D. S., Marshall, A. H. E., and Smith, F. B.
Microgliomatosis. A Form of Reticulosis Affecting the Brain 1

Russell, D. S., Russell Brain, W., and Greenfield, J. G.
Subacute Inclusion Encephalitis 365

Seyffarth, H., and Denny-Brown D.
The Grasp Reflex and the Instinctive Grasp Reaction 109

Sinclair, D. C., Weddell, G., and Feindel, W. H.
Referred Pain and Associated Phenomena 184

Smith, F. B., Russell, D. S., and Marshall, A. H. E.
Microgliomatosis. A Form of Reticulosis Affecting the Brain 1

Stanier, W. M., Mandelbrote, B. M., Thompson, R. H. S., and Thruston, M. N.
Studies on Copper Metabolism in Demyelinating Diseases of the Central Nervous System 212

Sunderland, S.
The Distribution of Sympathetic Fibres in the Brachial Plexus of Man 88

Sunderland, S., and Ray, L. J.
The Intraneural Topography of the Sciatic Nerve and its Popliteal Division in Man 242

Ter Braak, J. W. G., and Rademaker, G. G. J.
On the Central Mechanism of Some Optic Reactions 48

Thompson, R. H. S., Mandelbrote, B. M., Stanier, M. W., and Thruston, M. N.
Studies on Copper Metabolism in Demyelinating Diseases of the Central Nervous System 212

PAGE

Thruston, M. N., Mandelbrote, B. M., Stanier, W. M., and Thompson, R. H. S.
Studies on Copper Metabolism in Demyelinating Diseases of the Central Nervous System 212

Ward, J. W., and Clark, G.
Responses Elicited from the Cortex of Monkeys by Stimulation Through Fixed Electrodes 332

Weddell, G., Sinclair, D. C., and Feindel, W. H
Referred Pain and Associated Phenomena 184

NOTICE OF RECENT PUBLICATIONS.

Abnormal Psychology. J. D. Page 106
Clinical Psychology. C. Berg 476
Diseases of the Nervous System. Russell Brain 105
Harvey Cushing—A Biography. J. F. Fulton 103
Mongolism and Cretinism. C. E. Benda 108
Neocortex of Macaca Mulatta. Von Bonin and P. Bailey 104
Neuroanatomy. F. A. Mettler 476
Pathology of Tumours. R. A. Willis 107
Post-natal Development of the Human Cerebral Cortex. J. Le Roy Conel 106
Textbook of Clinical Neurology. I. Wechsler 105

SUBJECTS.

A and C Fibre Components in the Babinski Plantar Response and the Pathological Flexion Reflex, Demonstration of. E. Kugelberg 304
Aphasia and Artistic Realization. Th. Alajouanine 229
Centromedian Nucleus of the Human Thalamus, Projection of. T. McLardy 290
Copper and Iron Content of Brain and Liver in the Normal and in Hepatolenticular Degeneration. J. N. Cumings 410
Copper Metabolism in Demyelinating Diseases of the Central Nervous System. B. M. Mandelbrote, W. M Stanier, R. H. S. Thompson and M. N. Thruston 212
Cutaneous Hyperalgesia, Observations on. J. A. Harpman 34
Electroencephalography with Pharyngeal Electrodes. J. Roubicek and D. Hill 77
Foramen of Majendie in a Series of Human Brains, Observations on. Murray A. Barr 281
Grasp Reflex and Instinctive Grasp Reaction. H. Seyffarth and D. Denny-Brown 109
Gustatory Sweating. H. A. Haxton 16
Hereditary Ataxia and Peroneal Muscular Atrophy, On a Possible Relationship Between: with a Critical Review of "Intermediate Forms" in the Degenerative Disorders of the Central Nervous System. M. Roth ... 416
Intracisternal Injection of Saline Solutions on the Pressure of the Cerebrospinal Fluid in the Dog, The Effect of the. T. H. B. Bedford 403
Intraneural Topography of the Sciatic Nerve and its Popliteal Division in Man. S. Sunderland and L. J. Ray 242
Lipidoses and the Central Nervous System. Alan Bird 434
Lumbar Puncture Headache. G. W. Pickering 274
Microgliomatosis, a Form of Reticulosis Affecting the Brain. B. S. Russell, A. H. E. Marshall and F. B. Smith 1

PAGE

Olivo-ponto-cerebellar Atrophy. Macdonald Critchley and J. G. Greenfield 343

Optic Reactions, On the Central Mechanism of Some. G. C. J. Rademaker and J. W. G. Ter Braak 48

Posture of the Limbs, The Influence of Alteration in, on Cortically Induced Movements. E. Gellhorn 26

Referred Pain and Associated Phenomena. D. C. Sinclair, G. Weddell and W. H. Feindel 184

Representation in the Motor Cortex, The Mode of. G. Clark 320

Responses Elicited from the Cortex of Monkeys by Electrical Stimulation Through Fixed Electrodes. G. Clark and J. W. Ward 332

Sarcoidosis, with Involvement of the Nervous System. J. Colover 454

Subacute Inclusion Encephalitis. W. Russell Brain, J. G. Greenfield and Dorothy S. Russell 365

Sympathetic Fibres, The Distribution of, in the Brachial Plexus of Man. S. Sunderland 88

Thrombosis of Intracranial Veins. D. Kendal 386

Notices of Recent Publications 103, 476